Approach to Vomiting and Anti-Emetics

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Physiology of vomiting

Classically, vomiting can occur via humoral or neural pathways. The humoral pathway implies that the CRTZ is stimulated by bloodborne substances. The CRTZ is located in the area postrema outside the blood brain barrier; its location allows for contact with systemic circulation. Stimulation of the is region by endogenous and exogenous stimuli through specific receptors results in direct stimulation of the emetic center.

The neurologic pathway occurs from neurologic imput from the CRTZ, vestibular system, vagosymphatetic afferents and cerebral cortex. Local stimulation of vagal afferents through gastrointestinal disease result in direct communication with the nucleus tractus solius (NTS). The NTS is a group of nuclei located within the brainstem that receives imput from various organs for coordinated actions. In this case, stimulation of the NTS results in subsequent vomiting. In addition to local gastrointestinal stimulation, cerebral cortical imput through the NTS and emetic center is thought to be important in people and may play a role in some animals. Vestibular imput also stimulates vomiting through neural mechanisms, however, species differences do exist. Canine vestibular input indirectly stimulates the emetic center through the CRTZ which is directly stimulated. However, feline vestibular input directly stimulates the emetic center.

Pharmacology of vomiting

The interactions between afferent impulses and between regions of the brain involve various receptors that can be utilized clinically to induce and block emesis. Knowledge of these receptors helps to guide therapeutic interventions and develop novel medications.

A list of the respective receptors and neurotransmitters are listed below:

CRTZ

D2 (dopaminergic) (D>C)	Dopamine
A2 (adrenergic) (C>D)	Norepinephrine
5HT3 (serotonergic) (D, C)	Serotonin
M1 (cholinergic) (D, C)	Acetylcholine
H1 and H2 (histaminergic) (D)	Histamine
NK1 (neurokininergic) (D,C)	Substance P
ENKμ and ENKδ enkephalinergic) (D,C)	Encephalins

Dopamine: more important in the dog
Adrenergic: more important in the cat
Histaminergic: not appreciated in cats, only dogs

Emetic center

5HT1A	Serotonin
A2 (adrenergic)	Norepinephrine
NK1 (neurokininergic) (D,C)	Substance P

Vestibular center

M1	Acetylcholine
NK1	Norepinephrine
NMDA	Glutamate

M1 receptors are identified in cats and role is unclear
Vestibular efferents in the dog act on the CRTZ and on the emetic center in Dog

Cerebral Cortex

ENKμ and ENKδ (enkephalinergic)	Enkephalin
ω2	Benzodiazepines

These receptors play a more active role in people with anticipatory nausea in people. The role in animals is less certain and could play a role in some patients. Theoretically utilization of opiods or cannabinoids (ENK) or benzodiazepines (ω2) could aid in management in some patients.

Gut Afferents

5HT3	Seratonin

These receptors play a pivotal role in transmitting information regarding intestinal inflammation, irritation, erosions/ulceration, distension, etc. to the NTS which results efferent nerve impulses that result in vomiting (see below).

Gut Efferents:

5HT4	Seratonin
D2	Dopamine
M2	Acetylcholine
Motilin receptors	Motilin

These receptors are important for interactions on myenteric neurons for coordinated emesis. Once the emetic center is stimulated by humoral or neural mechanisms a coordinated set of events leading to vomiting occur. These events include: relaxation of the pyloric antral region, retrograde intestinal movement, dilation of the esophageal sphincters and gastric cardia. Subsequent inspiratory movements against a closed glottis (retching) results in generation of marked intrathoracic negative pressures which moves injesta into the esophagus. Vomiting is completed with abdominal contractions that result in positive intraabominal/thoracic pressures and expulsion of vomitus. Manipulation of these receptors are non-traditional. Furthermore these medications are not considered to be true antiemetics as there properties are motility modifying. However, in select patients, these medications may be helpful.

Commonly clinical findings of vomiting

It is critical to characterize the patient as vomiting. Clients will always default to vomiting and never report regurgitation. Therefore, it is critical to characterize each patient and maintain an open mind (as vomiting is considerably more common). It is important to note that some disorders can result in a mixed bag of signs (gastric outflow tract obstructions) and other patients may have both problems (ie. secondary esophagitis from vomiting). A careful history can help to characterize the primary disturbance and guide appropriate diagnostic considerations. When taking a history it is important that you avoid certain words like retching as owners will commonly say "yes" if vomiting or regurgitating. It is important to remember that regurgitation can be noisy ("esophageal borborygmus") and can look violent/active at times. You should learn to imitate vomiting and regurgitation, as this may eliminate confusion.

Vomiting	**Regurgitation**
Active abdominal contractions	Passive
Anticipatory nausea, withdrawal, behavioral changes (observed)	Generally not observed, however esophageal pain can result in nausea like signs
Digested food	Undigested food, may be tubular
Often associated with inappetance	Normal to ravenous (can be inappetant)
Bile may be present	Bile is absent
May have digested blood (rarely fresh blood)	Rarely has fresh blood
Nausea signs often present	"Nausea" signs (drooling, repetitive swallowing, etc.) are possible
Generally not associated with eating	May be associated with eating (etiology dependent)

Diagnostic approach

When presented with a patient that is vomiting some simple questions should be answered.

- Is it truly vomiting?
- Is if chronic or acute?
- Is the patient sick?
- Is the examination normal?

The relative need to perform diagnostic testing lies in the answers to these questions. Acute disease that is mild in nature may often times be treated symptomatically, whereas acute, severe cases call for further characterization. Chronic disease requires diagnostic decisions that eliminate disease processes from the differential diagnoses and serve to confirm the suspected diagnosis. Additionally, therapeutic decisions must serve to eliminate differential diagnosis and provide information about the potential etiology.

Classification

Primary gastrointestinal	Secondary gastrointestinal
Inflammatory gastroenteritis	Drug induced
Infectious gastroenteritis	Pancreatitis
Dietary indiscretion	Endocrine (hypoadrenocorticism,
Toxic	hyperthyroidism)
Neoplastic	Hepatobiliary disease
Foreign bodies	Renal failure
Structural (intussusception, torsions, adhesions, etc.)	Hypercalcemia
Ulcerations (local or paraneoplastic)	
Parasitic	
Food allergy/dietary intolerance	

Diagnostic considerations

CBC, chemistry, urinalysis
Cortisol, ACTH stimulation testing
TT4, fT4 testing
Serum bile acids
fPLI, cPLI
Abdominal radiographs (helpful for foreign material, obstructive patterns, etc.)
Abdominal ultrasound
Anti-helmintic trials
Dietary trials
Helicobacter therapy
Endoscopy
Abdominal CT

Medications

Phenothiazine antiemetics (prochlorperazine, chlorpromazine)

These medications have a broad spectrum effect with effects on the CRTZ, emetic center and on peripheral receptors. There effects are predominantly though to occur via A2 antagonism (CRTZ, emetic center), however D2 antagonism, H1 antagonism, and M1 antagonism concurrently play a role in there efficacy. These medications have additional properties, acting as a calcium channel antagonist that can alter intestinal secretion. Hypotension and sedation are potential negative attributes of these medications but are generally mild and rarely clinically significant. However, they should be avoided in already hypotensive patients.

Chlorpromazine	0.2-0.4 mg/kg q 8 SQ, IV 2mg PO q 12 (C) 4-8 mg PO q 12 (D)
Prochlorperazine	0.1-0.5 mg/kg q 6-8 SQ, IM, IV
Promethizine	2mg/kg PO, IM q 12-24??

D2 antagonists (metoclopramide, domperidone)

These medications act at the CRTZ and peripherally at gut smooth muscle. There central actions are only appreciated in the dog, as dopaminergic receptors are not important in the CRTZ of cats. Peripherally, it acts through smooth muscle sensitization to acetylcholine. The action on peripherally will result in increased gastric emptying and decreased intestinal transit times. Additionally, it will alter gastroesophageal sphincter (increased) and pyloric (decreased) tone.

Metoclopramide	0.2-0.4 mg/kg q 6 PO, SQ, IM, IV 1-2 mg/kg/day CRI (Give loading dose 0.2 mg/kg IV)

NK1 antagonists (maropitant)

Maropitant is a neurokinin-1 (NK_1) receptor antagonist which acts centrally and peripherally. Central blockade of substance P occurs at the CRTZ and emetic center. Peripherally substance P may play a role in visceral pain and vagal afferent transmission; inhibition of

emesis with peripherally induced emetics has been shown in dogs. While it does not affect gastrointestinal motility it can decrease intestinal contraction pressure patterns. Addiitonally, it has been shown to be effective at blocking motion sickness. It has been used safely in cats and more recently has been utilized intravenously.

Maropitant	1 mg/kg SQ, IV q24h (slow bolus of diluted with fluids) 2 mg/kg PO q24h (D) 1mg/kg PO q 24 (C) Travel sickness: 8 mg/kg orally, 2 hours before travel Vestibular disease: 8 mg/kg PO, IV

Serotonin (5-HT_2) receptor antagonists

These medications at both peripherally (vagal afferent neurons) and centrally (CRTZ). The medications seem to be more effective at blocking peripherally induced emesis. Classically, these medications have been given for chemotherapy induced nausea (platinum agents) as this is thought to be mediated through mucosal enterochromaffin cells release of serotonin locally within the small intestine in dogs and via the sertoninergic effects on the CRTZ in cats. These medications appear to be effective anti-emetics in various clinical conditions, however, pharmacologic evaluation of these drugs in companion animals has not been critically evaluated. Differences in species half-lives may optimize drug frequency.

Ondansetron	0.5–1 mg/kg orally q12–24h 0.5 mg/kg IV Loading dose, followed by 0.5 mg/kg/hr over 6 hours
Dolasetron	0.6-1 mg/kg IV, SQ, PO q 12-24
Granisetron	0.1–0.5 mg/kg PO or IV q12–24h

Mirtazapine has a multitude of actions. It likely acts central and peripherally to promote its anti-emetic/nausea properties via antagonism at the $5HT_3$ receptors. Additional properties of this medication include antagonism at central pre-synaptic $alpha_2$-receptors resulting in increased norepinephrine. This effect may contribute to antidepressant properties and appetite stimulant effects. Additionally, it possesses 5HT2, H1, alpha1 adrenergic and muscurinic receptor antagonism.

Mirtazapine	1.875 mg PO q 24-48 (renal patients) (C) 0.5-0.6 mg/kg PO q 24 (D) *don't exceed 30mg/day

Additional considerations

Meclizine is a piperizine antihistamine that has been used in dogs as an H1 antagonist. This effect is thought to block vestibular afferents on the CRTZ. These medications may not play a role in cats due to differences in physiology. It is thought that meclizine may have additional anticholinergic effects that could contribute to the antiemetic effect

Meclizine	25mg PO q 24 (D)

5HT1 receptor agonists have been used experimentally to reduce motion sickness and xylazine induced vomiting in cats. Buspirone could be considered in feline patients with refractory vomiting. Clinical use of buspirone for vomiting has not been extensively described.

Dexamethasone is utilized in people for chemotherapy-induced nausea and vomiting (CINV). The mechanism of action is uncertain but appears to be indicated predominantly for moderate to severely emetogenic chemotherapy.

Butorphanol has been given to animals for its antagonism of enkephalinergic receptors within the CRTZ and most commonly administered to patients for chemotherapy induced emesis/nausea.

Cannibinoids have been given to people to affect the cerebral cortical encephalinergic receptors with CINV. In some cases, these compounds are found to be more effective then other classes of antiemetics in people. The clinical utility in veterinary medicine is uncertain.

Gastroprotectants can be indicated for patients with ulcerogenic or erosive gastritis/duodenitis. These medications will reduce acid secretion or adhere to mucosal defects, thus reducing exposure of acid to denuded gastroduodenal wall. These medications are generally reserved for patients that have concurrent esophagitis or presence of hematemesis. Routine use of these medications in vomiting patients is not likely indicated. These medications can interfere with drug absorption (ie. Carafate) or interfere with hepatic clearance of other compounds via P450 interference (ie. omeprazole, ranitidine)

Non selective cholinergic receptor antagonists (atropine, scopolamine, aminopentamide, isoprpopamide) have been used may help to mitigate vomiting from M1 and M2 receptor antagonism. While these medications may be effective, M2 inhibition can result in

paralytic ileus and delayed gastric emptying. These medications should be used conservatively and are generally not recommended. M1 selective agents could be helpful for vestibular disease/motion sickness in dogs but are not readily available (ie. Pirenzipine).

Propofol has been used at subhypnotic doses to control refractory vomiting and nausea experimentally and clinically in humans. It is predominantly reserved for refractory CINV or for postoperative nausea and vomiting (PONV). The effect does not appear to block apomorphine induced emesis in humans. The role of this medication has not been evaluated in companion animals.

Motility modification may be indicated for some patients that are vomiting. See notes on "motility modification". These compounds may influence vomiting by reducing gastroduodenal reflux (ie. bilious vomiting syndrome), altering gastric emptying (patients with non-mechanical delayed gastric emptying) or altering intestinal transit time. Delayed gastric emptying and gastrointestinal distension may result in peripheral stimulation of enteric innervation and contribute to vomiting in some patients.

Non-pharmacologic considerations

- Address underlying disease processes
- Consider dietary manipulation of gastric motility