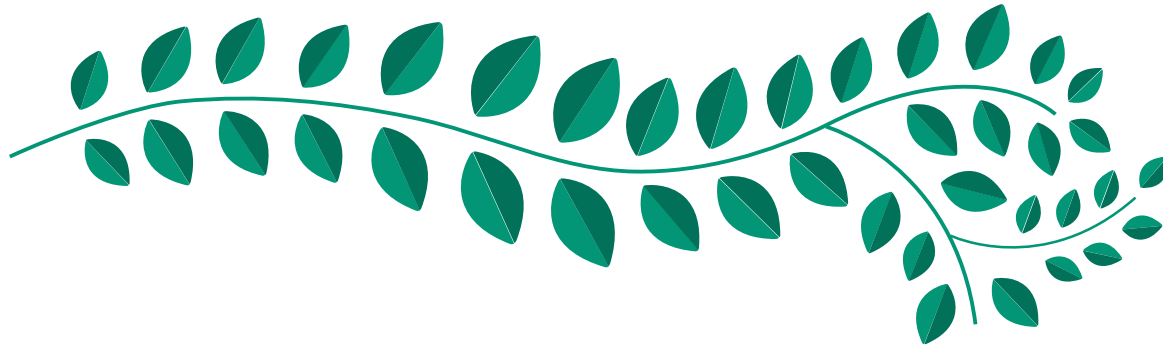


Drugs Acting on Gastrointestinal Tract

Tim Farmakologi Veteriner
FKH UB 2020



Physiology-Anatomy of GI Tract



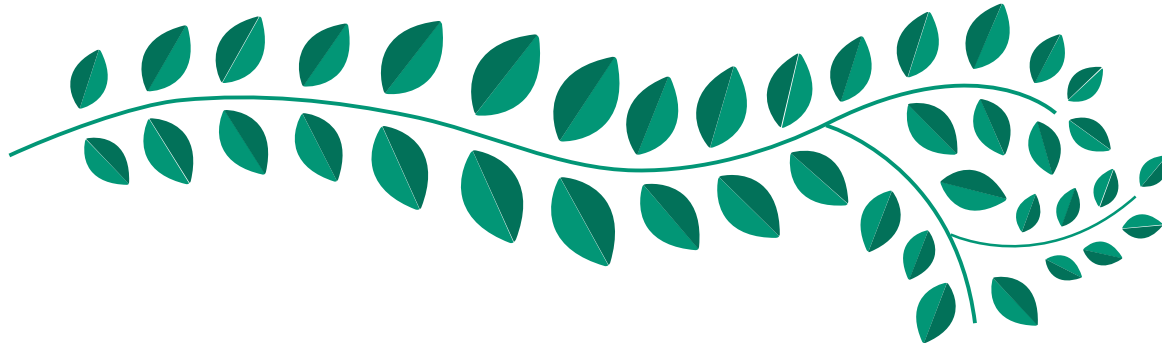
Physiology-Anatomy of GI Tract

- The anatomic structures therein include the oral cavity, pharynx, esophagus, stomach, small intestine, and large intestine.
- the digestive tract plays a role of bringing life-sustaining elements into the body, and taking waste products out of it.
- accessory organs (e.g., liver, gall bladder, salivary glands, and pancreas)

Physiology-Anatomy of GI Tract

- Regulation of these actions is controlled by many mechanisms.
- One control mechanism of the GI tract is the autonomic nervous system (ANS), which consists of the sympathetic branch (fight-or-flight response) and the parasympathetic branch (homeostatic response).
- Parasympathetic stimulation increases intestinal motility and GI secretions and relaxes sphincters.
 - **Cholinergic drugs** simulate these actions.
 - **Anticholinergic drugs** inhibit these actions.
- Sympathetic stimulation decreases intestinal motility, decreases intestinal secretions, and inhibits the action of sphincters.
 - **Sympathetic drugs** simulate these actions.

Drugs used for Gastrointestinal Disorder



Gastrointestinal Drugs Used in Veterinary Medicine

- Veterinary gastrointestinal drugs can be administered for a variety of reasons.
- Some gastrointestinal drugs encourage peristalsis, suppress it, or reduce its undesirable by-products.
- Other GI drugs decrease the flow of saliva, control vomiting and diarrhea, loosen stool, cause vomiting, protect the GI tract, decrease acid production, or reestablish GI normal flora.

Gastrointestinal Drugs

Drugs Used in Acid-Peptic Disease

Drugs That Promote Upper Gastrointestinal Motility

Emetics and Antiemetic Agents

Laxatives

Antidiarrheal Agents

Pancreatic Enzyme Replacements

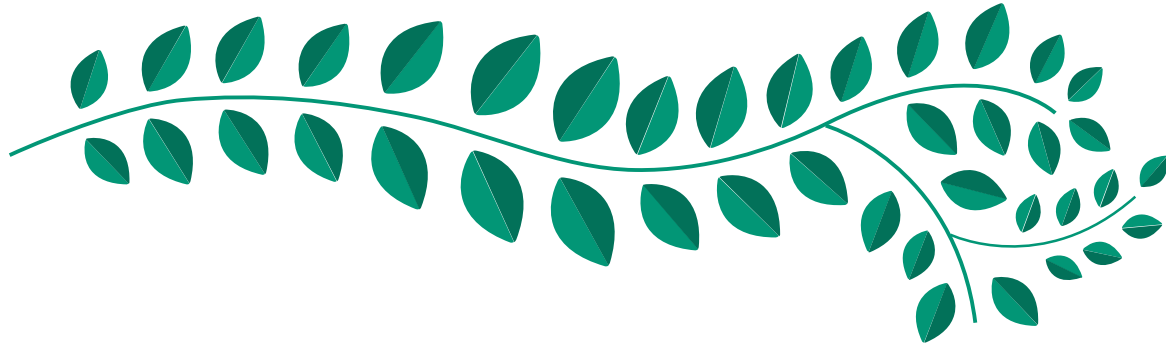
Appetite Stimulating Drugs

Gastrointestinal Drugs

- Drugs Used in Acid-Peptic Disease
- Motility Promoter
- Other Agents



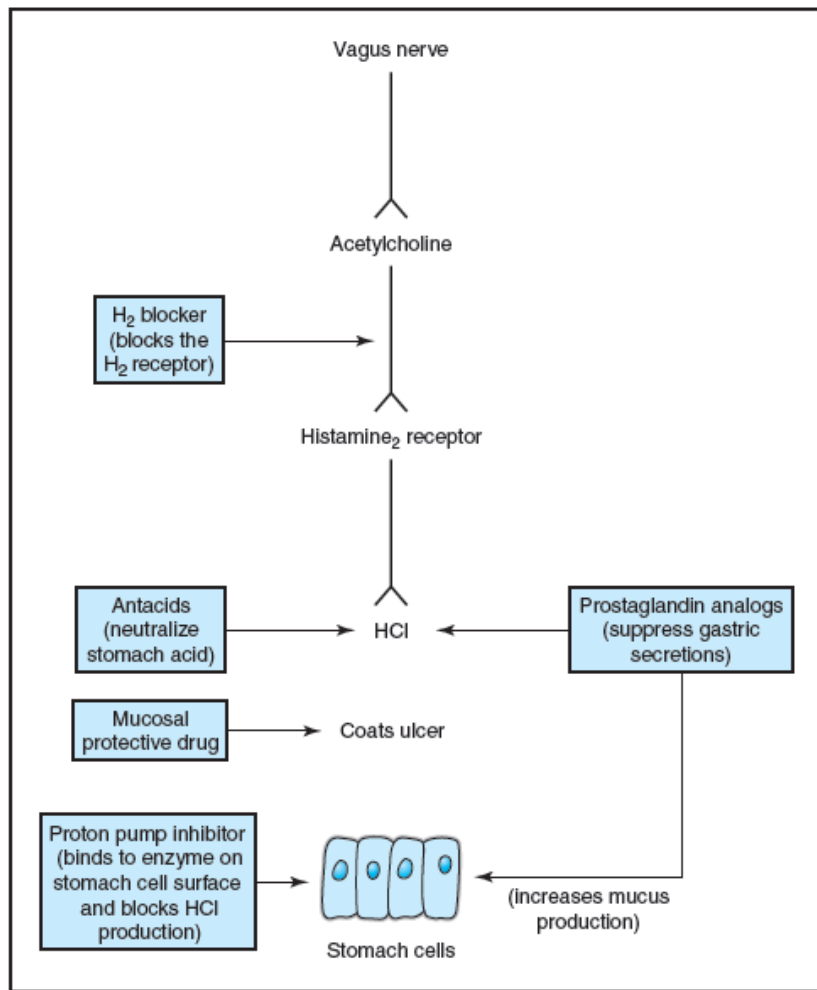
Drugs Used in Acid-Peptic Disease



Acid Peptic Disease



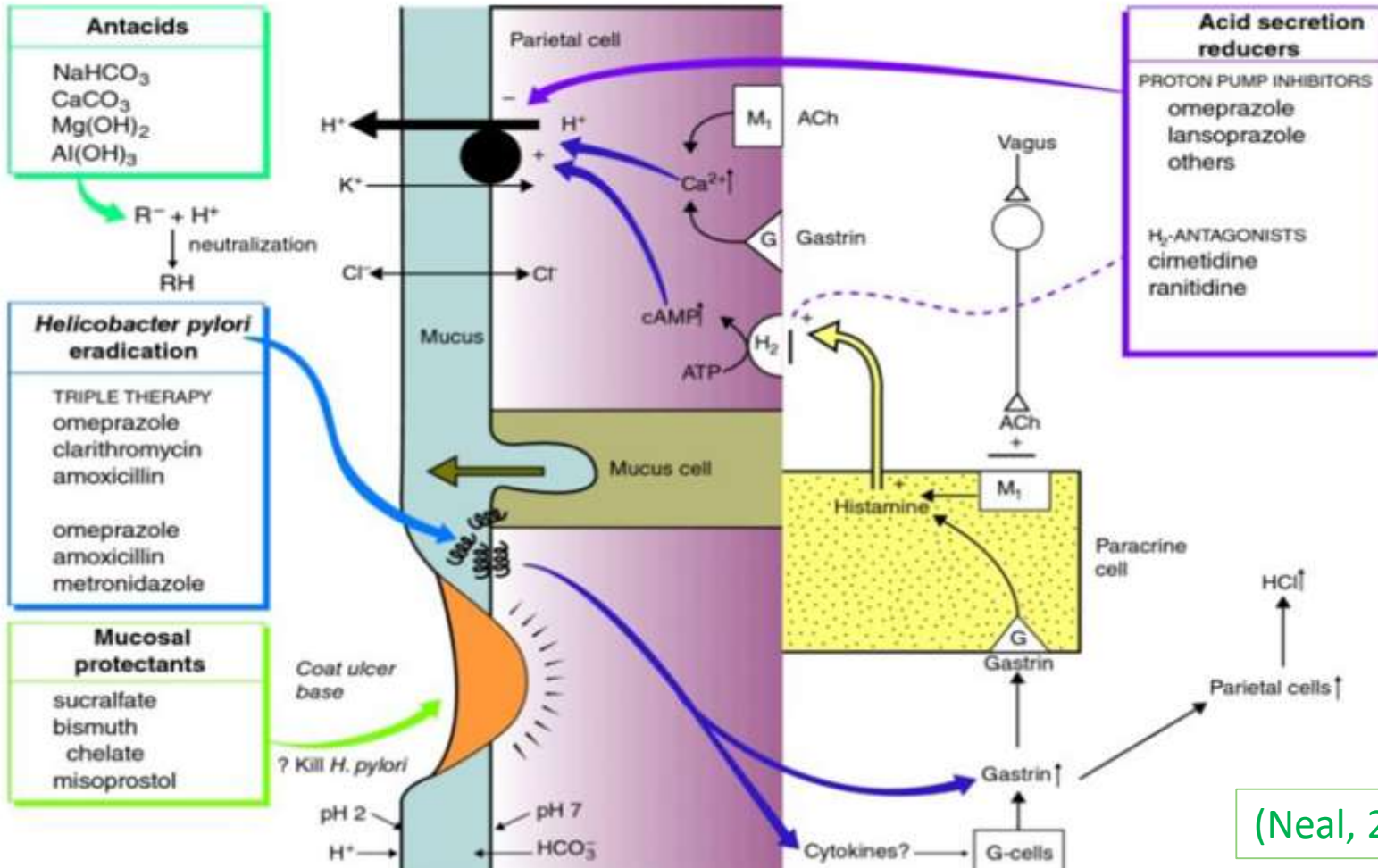
- Beberapa gangguan/penyakit yang melibatkan erosi/ulcer pada mukosa traktus GI, termasuk GERD, gastric and duodenal ulcers, nonulcer dyspepsia, and stress-related gastritis
- Sebagian kasus merupakan akibat dari peningkatan sekresi asam hidroklorid dari sel parietal lambung.
- Sel parietal dipengaruhi oleh histamine, gastrin, dan asetilkolin



Debra Cengage Learning

Figure 11-8 Mechanism of action of antiulcer drugs.

Drugs acting on the gastrointestinal tract I: peptic ulcer



(Neal, 2016)

Terapi pada Peptic Ulcer

Mengurangi sekresi asam lambung

- Antacid
- H₂-histamine antagonist
- Proton pump inhibitor

Meningkatkan resistensi mukosa

- Mucosal protectant

Eradikasi bakteri *Helicobacter pylori*

- Proton pump inhibitor
- Antibiotik

Acid secretion reducer

Histamine H₂-receptor Antagonists

- Cimetidine
- Ranitidine

Proton pump inhibitor

- Omeprazole
- Lanzoprazole

Antacids

- Sodium bicarbonate
- Magnesium hydroxide
- Aluminium hydroxide

Histamine H2-receptor antagonists

- Histamine-2 (H2) receptor antagonists prevent acid reflux by competitively blocking the H2 receptors of the parietal cells in the stomach, thus reducing gastric acid secretion.
- Example : *cimetidine* (Tagamet[®]), *ranitidine* (Zantac[®]), *famotidine* (Pepcid[®]), *nizatidine* (Axid[®])

Histamine H₂-receptor antagonists

- *cimetidine* (Tagamet®), the first H₂ blocker developed. It comes in tablet, oral solution, and injectable forms.
- *ranitidine* (Zantac®), which is more potent and has a longer duration of action than cimetidine. It is also available in tablet, oral solution, and injectable forms.
- *famotidine* (Pepcid®), which is more potent and has fewer side effects than ranitidine, but is less bioavailable. It is available in coated tablets, oral powder, and injectable forms.
- *nizatidine* (Axid®), which is an H₂-receptor antagonist and also has prokinetic action (see the following section on prokinetic agents) via

Antacids

- Substances that promote ulcer healing by neutralizing HCl and reducing pepsin activity.
- Antacids can interact with other drugs
 - by adsorption or binding of the other drugs (decreasing oral absorption of bound drug)
 - by increasing stomach pH (causing a decrease in absorption of certain drugs)
 - by increasing urinary pH (inhibiting elimination of drugs that are weak bases).
- Antacid use in animals has decreased due to difficulty of administration and the introduction of histamine-2 blockers

Antacids

Sistemic

- Sodium bicarbonate
- Calcium carbonate
- Not frequently used as an antacid in vet.medicine

Non-sistemic

- Magnesium hydroxide
- Aluminium/magnesium hydroxide
- Aluminium hydroxide



Non-systemic Antacids

- *magnesium hydroxide* (Magnalax[®], Rulax II[®], Milk of Magnesia[®]). In ruminants, magnesium hydroxide is used to increase rumen pH and as a laxative to treat rumen acidosis (grain overload). Magnesium-containing antacids are contraindicated in animals with kidney disease because they may develop electrolyte imbalances
- *aluminum/magnesium hydroxide* (Maalox[®], Mylanta[®]). In dogs and foals, aluminum/magnesium hydroxide may be used as an adjunctive treatment for gastric ulcers.
- *aluminum hydroxide* (Amphojel[®]). Aluminum hydroxide has also been used to lower high serum phosphate levels because it binds and thereby depletes phosphorus.

Mucosal Protective Drugs

- Mucosal protective drugs, also known as pepsin inhibitors, are typified by the drug *sucralfate* (Carafate®).
- Sucralfate is a chemical derivative of sucrose that is nonabsorbable and combines with protein to form an adherent substance that covers the ulcer and protects it from stomach acid and pepsin.
- Sucralfate comes in 1-g tablets, and its only side effect is constipation.
- Because sucralfate binds to ulcers in an acid environment, it should not be given at the same times as H₂ receptor antagonists.

Prostaglandin Analogs

- Prostaglandin analogs appear to suppress gastric secretions and increase mucus production in the GI tract.
- An example of a prostaglandin analog is *misoprostol* (Cytotec[®])
 - an oral tablet that is usually given to animals taking nonsteroidal anti-inflammatory drugs (NSAIDs).

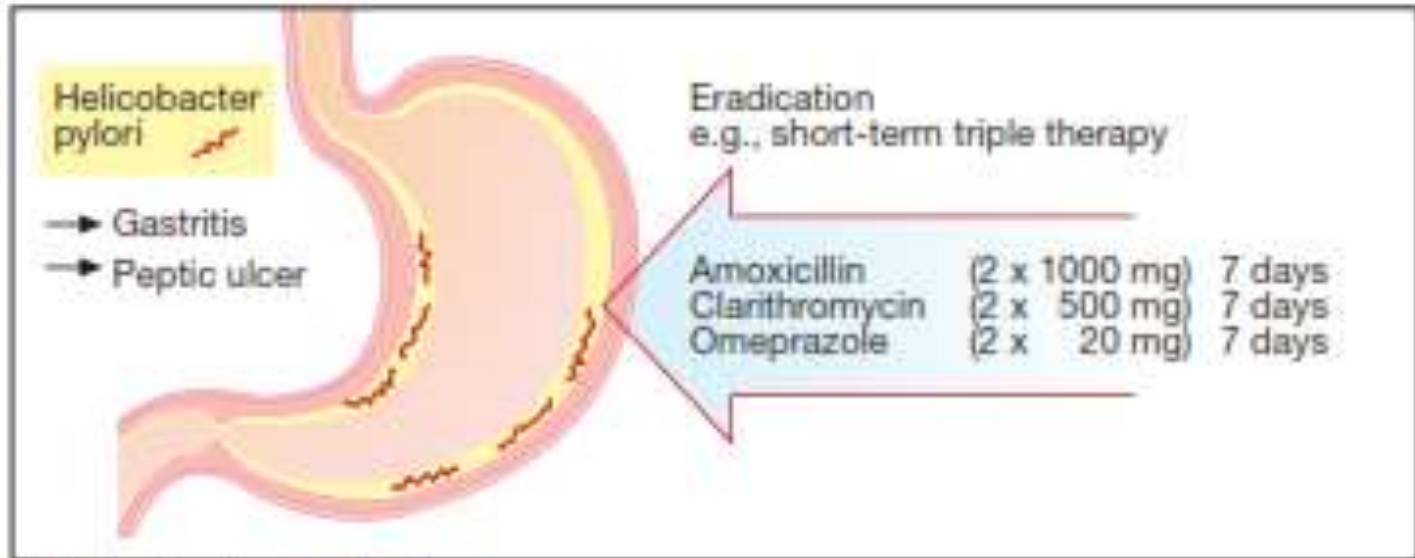
Proton Pump Inhibitors

- Proton pump inhibitors are drugs that bind irreversibly to the H⁺-K⁺-ATPase enzyme on the surface of parietal cells of the stomach.
- This inhibits hydrogen ion transport into the stomach so that the cell cannot secrete HCl.
- When this enzyme is blocked, acid production is decreased, and this allows the stomach and esophagus to heal.

Proton Pump Inhibitors

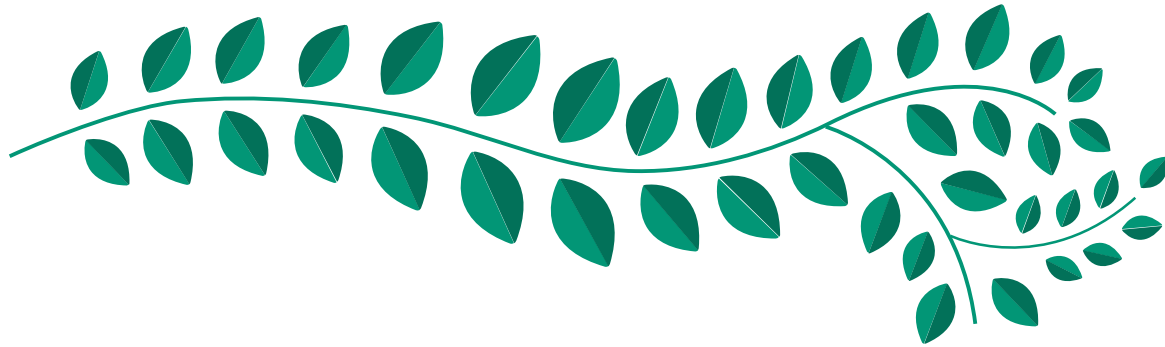
- *omeprazole* (Prilosec[®], Gastrogard[®]). In horses and foals more than four weeks of age, omeprazole is used to heal gastric ulcers and to prevent recurrence. Gastric ulcers in horses form secondary to feeding problems (too little hay intake), training (intense exercise increases gastric acid production), and changes with growth (a developing stomach may be injured by acid and enzymes). Gastric ulcers in horses interfere with performance.
- *lansoprazole* (Prevacid[®]), used to treat gastroesophageal reflux disease and to help heal gastric and duodenal ulcers. It blocks the last step of gastric acid production and is used extra-label in animals. Lansoprazole is less likely to react with other drugs than omeprazole.

Helicobacter Pylori Eradication



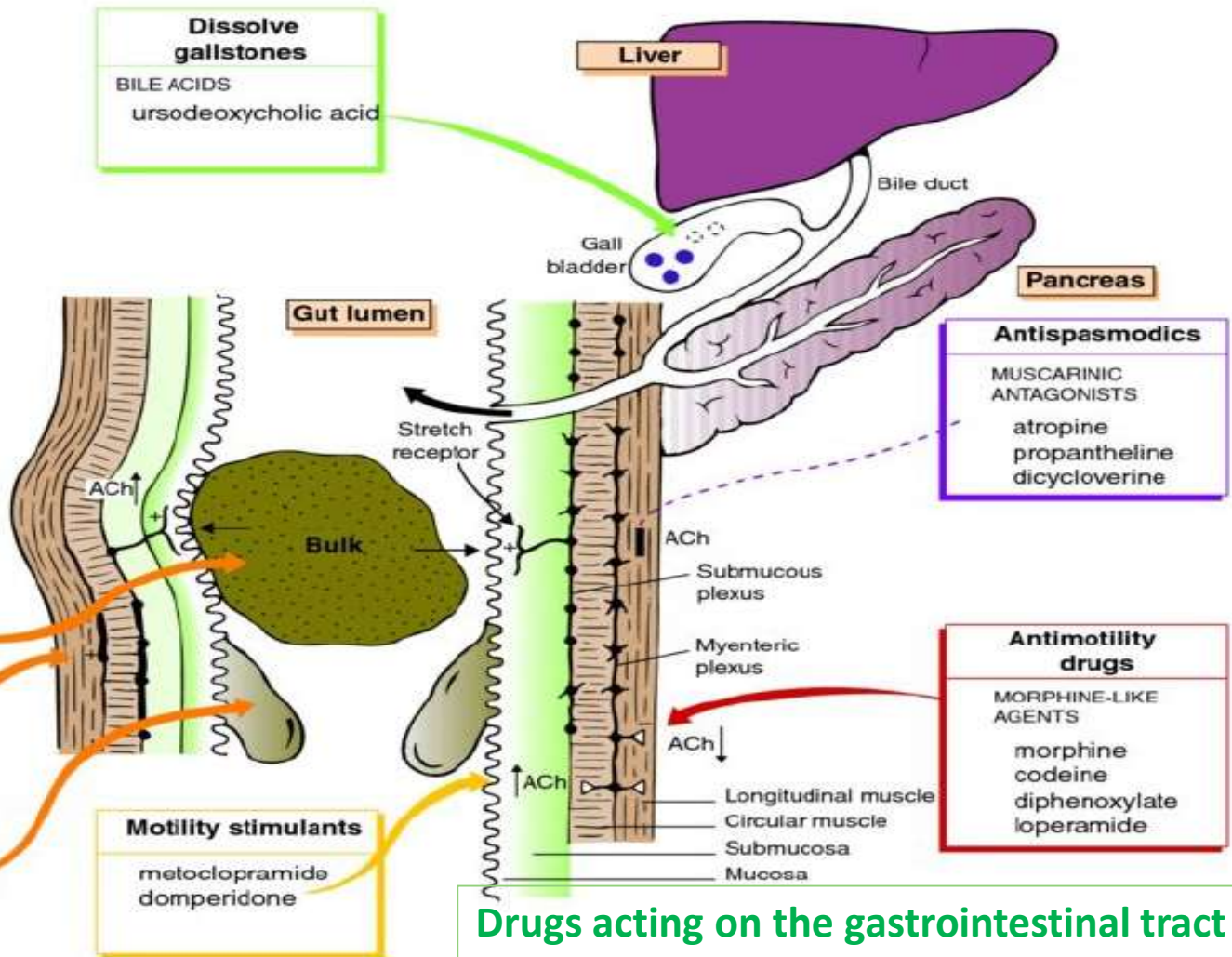
C. Helicobacter eradication

Drugs That Promote Upper Gastrointestinal Motility



- Drugs used in inflammatory bowel disease**
- Anti-inflammatory drugs**
- CORTICOSTEROIDS
 - hydrocortisone
 - prednisolone (suppositories, enemas, foam)
 - oral prednisolone
- Aminosalicylates**
 - sulfasalazine
 - mesalazine
- Pancreatic supplements**
 - pancreatin
- Laxatives**
- BULK
 - bran
 - ispaghula
- OSMOTIC
 - MgSO₄
 - lactulose
- STIMULANT
 - senna
 - bisacodyl
 - docusate
 - glycerol
 - suppositories
- FAECAL SOFTENERS (docusate)
 - arachis oil (enema)

- Dissolve gallstones**
- BILE ACIDS
 - ursodeoxycholic acid



Drugs acting on the gastrointestinal tract : motility and secretions (Neal, 2016)

Motility stimulants

- **Prokinetic agents** increase the motility of parts of the GI tract to enhance movement of material through it.
- **Parasympathomimetic agents, dopaminergic antagonists, and serotonergic agents** may act as prokinetics.



Parasympathomimetic Agents

Acetylcholinesterase inhibitors

- **Neostigmine** (Prostigmin®)
- It works by competing with acetylcholine for acetylcholinesterase, resulting in increased intestinal tone and salivation.
- Treatment of rumen atony
- Diagnosis of myasthenia gravis in dogs

Cholinergics

- **Dexpanthenol** (d-panthenol injectable, Ilopan®)
- Treatment of intestinal distention or atony, paralytic ileus, and colic.
- Post surgery treatment to increase gastric motility

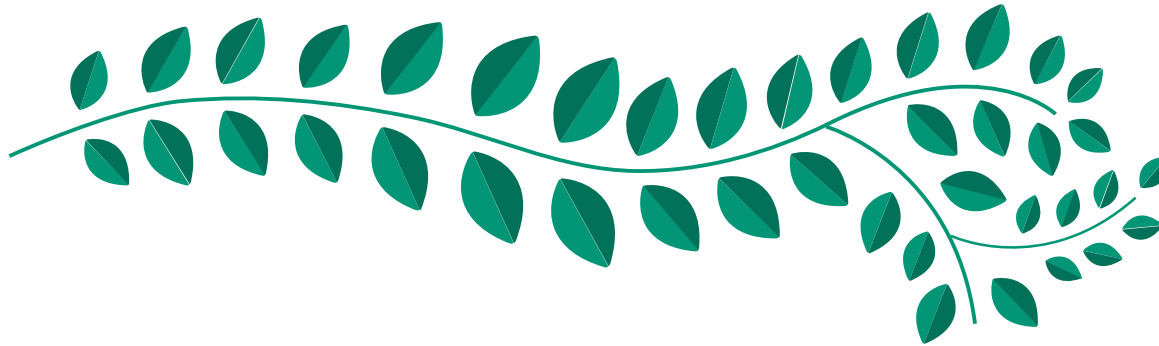
Dopaminergic Antagonists

- Dopaminergic antagonists stimulate gastroesophageal sphincter, stomach, and intestinal motility by sensitizing tissues to the action of the neurotransmitter acetylcholine.
- Side effects are behavioral in nature.
- Examples of dopaminergic antagonists include *metoclopramide* (Reglan[®]) and *domperidone* (Motilium[®]).

Serotonergic Agents

- Serotonergic agents stimulate motility of the gastroesophageal sphincter, stomach, small intestine, and colon.
- **Cisapride** (Propulsid[®]), used for the treatment of constipation, gastroesophageal reflux, and ileus.
- Side effects may include diarrhea, megacolon, and abdominal pain.

Emetic and Antiemetics Agents



1. Emetics

- Drugs that induce vomiting.
- Emetics are used in the treatment of poisonings and drug overdoses.
 - But NOT for caustic agent poisoning
- Emetics may be centrally acting (working on the CRTZ) or peripherally acting (working on receptors locally).

Emetics

- ***Apomorphine*** (Apokyn[®])
 - It is a morphine-derived emetic which stimulates dopamine receptors in the CRTZ and thus induces vomiting.
 - It is the emetic of choice for dogs
- ***Xylazine*** (Rompun[®], Gemini[®], AnaSed[®])
 - Induces vomiting in cats as a side effect of its use as a sedative.
 - The mechanism of emetic action is not fully understood for xylazine.
 - It is considered the emetic of choice for cats.

Emetics

- *Ipecac syrup*, which is made from roots and rhizomes of plants
- Two alkaloids, emetine and cephaeline, cause irritation to the gastric mucosa and centrally stimulate the CRTZ.
- It is usually used in dogs and cats.
- Ipecac can cause cardiovascular problems with higher doses.



Carapichea ipecacuanha (Brot.) L.

2. Antiemetics Agent

- Vomiting represents a coordinated effort of the gastrointestinal, musculoskeletal, and nervous systems to expel food, fluid, or debris from the gastrointestinal tract.
- The act of vomiting is controlled by the vomiting center in the medulla of the brain stem.
- Acetylcholine is the neurotransmitter for the vomiting center.

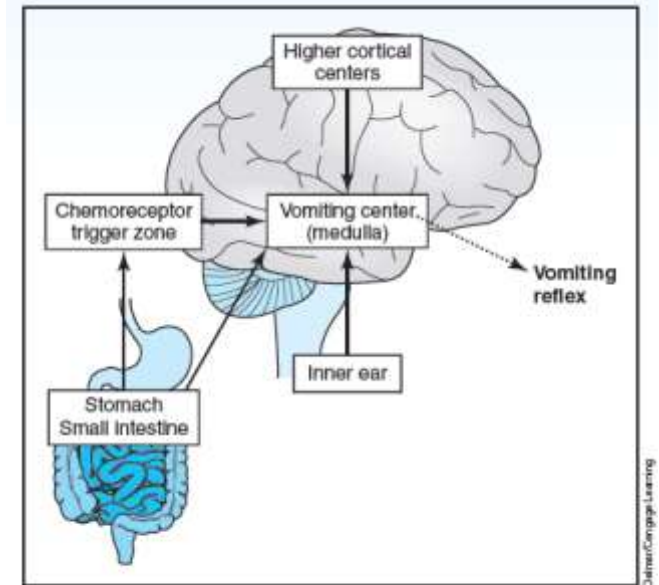


Figure 11-6 The vomiting center and factors that control vomiting

(Romich, 2010)

Type of Antiemetics

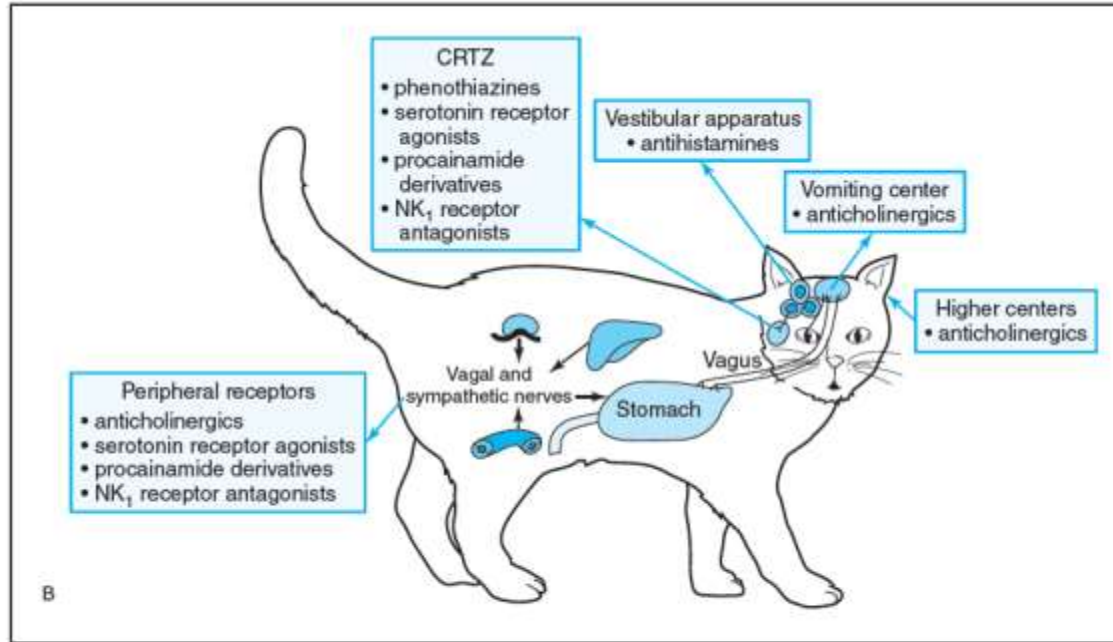


Figure 11-7 (A) Sites and neurotransmitters that mediate vomiting. (B) Sites of action of antiemetic drugs.

- **Phenothiazine Derivatives**
- **Antihistamines**
- **Anticholinergics**
- **Procainamide Derivatives**
- **Serotonin Receptor Antagonists**
- **Neurokinin (NK1) Receptor Antagonists**

Phenothiazine Derivates

- This group of drugs works by inhibiting dopamine in the CRTZ, thus decreasing the stimulation to vomit.
- Side effects include hypotension and sedation.
- Contraindication : abnormal gastrointestinal motility (because it may promote ileus and worsen vomiting).
- Example : *acepromazine, chlorpromazine, prochlorperzine, perphenazine*

Antihistamines

- Antihistamines are used to control vomiting in small animals when the vomiting is due to motion sickness, vaccine reactions, or inner ear problems.
- They work by blocking input from the vestibular system to the CRTZ.
- Antihistamines can cause sedation.
- Example : *trimethobenzamide, dimenhydrinate, diphenhydramine, meclizine*

Anticholinergics

- Anticholinergics block acetylcholine peripherally, which decreases intestinal motility and secretions.
- These drugs also decrease gastric emptying, which may increase the tendency to vomit.
- Contraindication : glaucoma or pyloric obstruction
- Example : *aminopentamide, atropin, propantheline*

Procinamide Derivatives

- This group of antiemetics works both:
 - centrally, by blocking the CRTZ (as a dopamine antagonist),
 - peripherally, by speeding gastric emptying, strengthening cardiac sphincter tone (decreasing gastroesophageal reflux), and increasing the force of gastric contractions.
- Contraindication : GI obstructions, GI perforation, or hemorrhage.
- Example : *metoclopramide* (Reglan[®])
 - It stimulates motility of the upper gastrointestinal tract without stimulating the production of gastric, biliary, or pancreatic secretions.

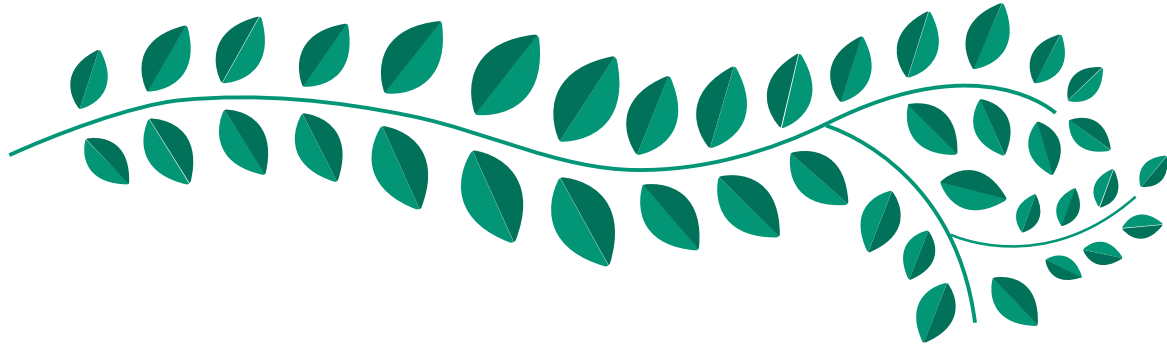
Serotonin Receptor Antagonists

- Serotonin receptor antagonists work selectively on 5-HT₃ receptors, which are located peripherally (on nerve terminals of the vagus nerve) and centrally (in the CRTZ).
- Blocking the release of serotonin from these sites controls vomiting.
- Example : **ondansetron** (Zofran[®]), **dolasetron** (Anzemet[®]), and **granisetron** (Kytril[®]).

Neurokinin (NK1) Receptor Antagonists

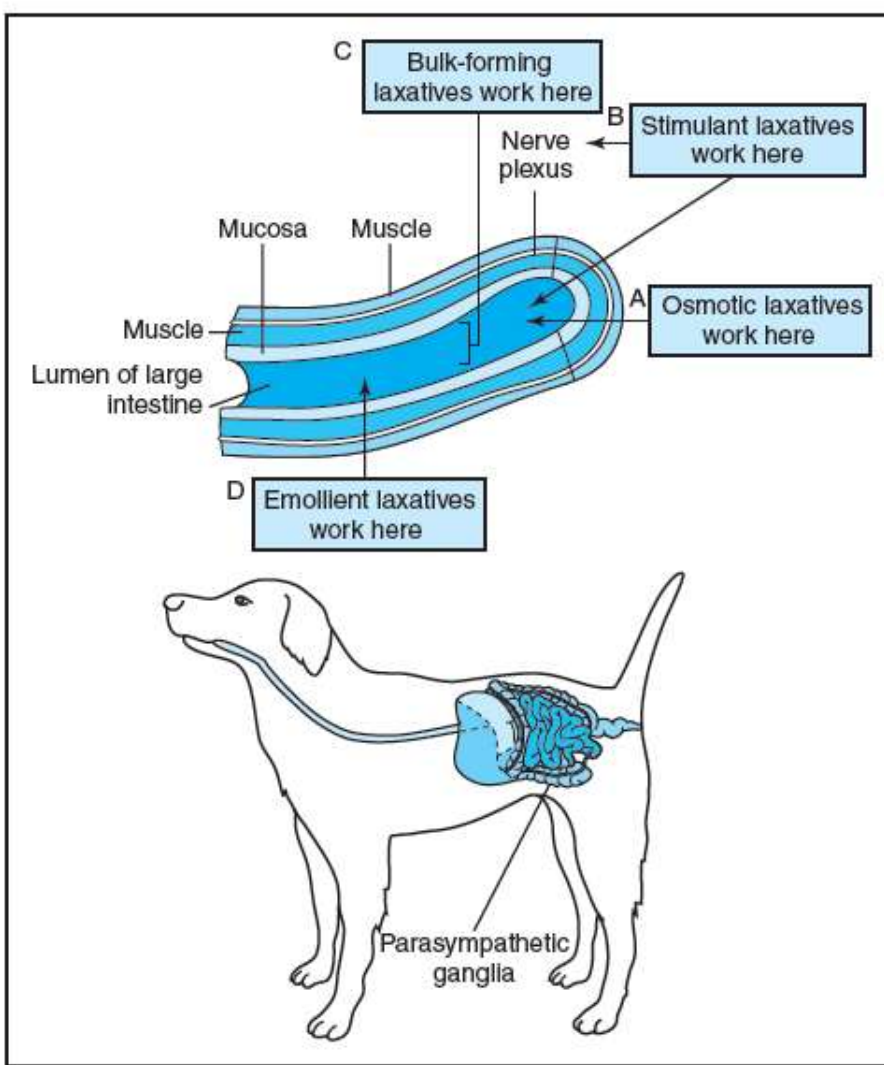
- Work on NK1 receptors, which are located in the vomiting center of the brain.
- These drugs work by inhibiting substance P, the key neurotransmitter involved in vomiting.
- Example : *maropitant citrate* (Cerenia[®])
 - Maropitant citrate is used to prevent acute vomiting and motion sickness

Other Agents



1. Laxatives

- A **laxative** is a medicine that loosens the bowel contents and encourages evacuation of stool.
- Veterinarians use laxatives to help animals evacuate stool without excessive straining, to treat chronic constipation from nondietary causes and movable intestinal blockages (such as hair balls), and to evacuate the GI tract before surgery, radiography, or proctoscopy.



- Bulk laxatives
- Osmotic laxatives
- Stimulant laxatives
- Emollient laxatives (Faecal softeners)

Bulk Forming

- The bulk-forming laxatives are natural fibrous substances or semisynthetic compounds that absorb water into the intestine, increase fecal bulk, and stimulate peristalsis, resulting in large, soft stool production.
- Tend to produce normally formed stools.
- *psyllium hydrophilic mucilloid* (Metamucil[®], Equine Psyllium[®], Perdiem[®])
- *polycarbophil* (FiberCon[®], Fiberall[®])
- *bran*

Osmotic (or hyperosmolar)

- Include salts or saline products, lactulose, and glycerin.
- Contraindication : heart failure and renal dysfunction
- Hyperosmolar salts pull water into the colon and increase water content in the feces, increasing bulk and stimulating peristalsis
- ***lactulose*** (Cephulac[®]), also used in liver disease because it eliminates ammonia

Stimulant

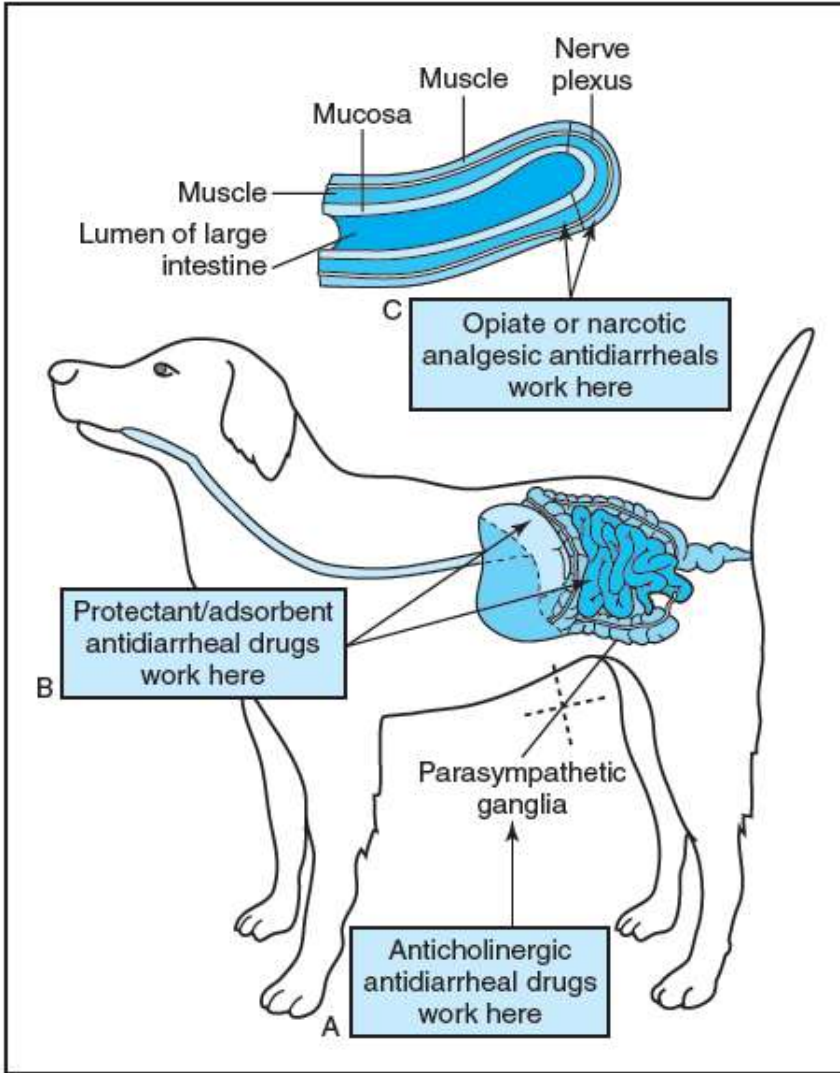
- Stimulant (irritant or contact) laxatives increase peristalsis by chemically irritating sensory nerve endings in the intestinal mucosa.
- **bisacodyl** (Dulcolax[®]), a cathartic that comes in enteric-coated and suppository forms.
- **castor oil** (active ingredient : ricinoleic acid). Ricinoleic acid inhibits water and electrolyte absorption, leading to fluid accumulation in the gastrointestinal tract and increased peristalsis.

Emollients

- Emollients are stool softeners which reduce stool surface tension and reduce water absorption through the colon, increasing water retention in stool and mixing of fats and fluid with the fecal mass.
- Resulting in a softer stool that is more easily passed.
- Emollients are not absorbed systemically, and thus have fewer side effects.
- **Docusate sodium**

2. Antidiarrheal Agents

- **Antidiarrheals** are drugs that decrease peristalsis of the gastrointestinal tract, thereby allowing fluid absorption from the intestinal contents.
- This helps to reverse diarrhea by decreasing the liquidity of stool.
- Antidiarrheals include anticholinergics, protectants, adsorbents, and narcotic analgesics



- **Anticholinergic**
- **Opiate or narcotic analgesic**
- **Protectant/adsorbent**

(Romich, 2010)

Anticholinergic

- Anticholinergics are used to treat tenesmus (straining to defecate) associated with colitis and vomiting related to colonic irritation.
- Decreasing gastrointestinal motility and secretions.

- *atropine* (generic, Atropine Injectable-SA[®], Atropine Injectable-LA[®]), which is available as an injection to decrease gastrointestinal motility in many animal species (atropine also has a wide variety of other actions that are covered in the appropriate chapters).
- *aminopentamide* (Centrine[®]), which is available in tablet and injection form, for treatment of acute abdominal spasm in dogs and cats.
- *propantheline* (Pro-Banthine[®]), which is available as tablets, is used to treat gastrointestinal spasms and hypersecretions associated with colitis and irritable bowel syndrome in dogs and cats and to reduce rectal contractions in horses.
- *methscopolamine* (Biosol-M[®]), which is available as a liquid, is a product that has antispasmodic properties and an antibiotic (neomycin) that is used to treat bacterial diarrhea in dogs and cats.
- *N-butylscopolammonium bromide* (Buscopan[®]), which is available in injection form, is an anticholinergic used as a single IV dose in horses with spasmodic colic, flatulent colic, or simple impactions.

Protectants/Adsorbents

- This category of antidiarrheal drugs works either by coating inflamed intestinal mucosa with a protective layer (**protectants**), or by binding bacteria and/or digestive enzymes and/or toxins to protect intestinal mucosa from their damaging effects (**adsorbents** bind substances).

- *bismuth subsalicylate* (Corrective Mixture[®], Pepto-Bismol[®]). The bismuth portion of this drug coats the intestinal mucosa and has antiendotoxic and weak antibacterial effects. The subsalicylate portion has anti-inflammatory effects because it reduces the production of prostaglandins. Subsalsicylate is an aspirin-like product; therefore, this drug should not be used in cats. Corrective Mixture with Paregoric[®] has an opium tincture in it and is a C-V controlled substance. These products can blacken stool and can also cause opacities on radiographs.
- *kaolin/pectin* (Kao-Forte[®], Kaopectolin[®], K-P-Sol[®]). This combination drug has both adsorbent and protective qualities. Bacteria and toxins are adsorbed in the gut and the coating action protects inflamed intestinal mucosa.
- *activated charcoal* (Liqui-Char[®], Superchar[®], Actidose-Aqua[®]). Activated charcoal is a fine, black, tasteless powder used to adsorb many chemicals and drugs in the upper gastrointestinal tract. It is used primarily to treat ingestions of certain toxins and is typically administered via stomach tube, dosing gun, or premeasured syringe (Figure 11-4).

Opiate or Narcotic Analgesic

- Opiates or narcotic analgesics control diarrhea by decreasing both intestinal secretions and the flow of feces, and increasing segmental contractions, thereby resulting in increased intestinal absorption.
- Side effects of these drugs include CNS depression (excitement in horses and cats), ileus, urinary retention, bloat, and constipation with prolonged use.

- *diphenoxylate* (Lomotil[®], Lonox[®], Diphenatol[®]), a C-V controlled substance with atropine added. Diphenoxylate is not an opium derivative, but is structurally similar to meperidine.
- *loperamide* (Imodium[®], Imodium A-D[®]). This drug causes less CNS depression than other drugs in this category and can be purchased over the counter. Like diphenoxylate, it is structurally similar to meperidine.
- *paregoric*. This drug is a C-III controlled substance and may be combined with kaolin/pectin. Paregoric is camphorated tincture of opium.

Probiotics

- *Lactobacillus* spp., *Enterococcus faecium*, and *Bifidobacterium* spp.
- The mechanisms of action of probiotics may involve competing with pathogenic bacteria for colonizing sites, production of antimicrobial factors, alteration of the microenvironment, reduction of local inflammation, and alteration of immune responses.
- Plain yogurt, Fastrack[®] gel, FortiFlora[®], Proviabio[™]-DC, dsb.

Anaerobic antibiotics

- **Metronidazole** (Flagyl[®]) is an antibiotic that is effective against anaerobic bacteria.
- Metronidazole is effective against anaerobes, it may help return the animal's stool to its normal consistency.

3. Pancreatic Enzyme Replacements

- Pancreatic exocrine insufficiency (PEI) is a disease in which the pancreas does not produce digestive enzymes.
- These enzymes can be supplemented in the diet through the use of pancrealipase.
- ***Pancrealipase*** (Viokase[®]-V Powder, Pancrezyme[®]) contains primarily lipase (enzyme that digests fats), but also has amylase (enzyme that digests starch) and protease (enzyme that digests proteins) to help with digestion of fats, starch, and protein.

4. Appetite Stimulating Drugs

- For anorexic animals that do not respond to coaxing with small amounts of palatable foods, drug therapy may be used to stimulate appetite.
- **Serotonin antagonist antihistamines**
- **Benzodiazepines**
- **Progestins**
- **Glucocorticoids**

Serotonin antagonist antihistamines

- Drugs that compete with histamine for sites on H1 receptors on effector cells
 - not by blocking histamine release, but antagonizing its effects
 - promote appetite by inhibition at the serotonergic receptors, which normally control satiety (fullness)
- Example : *cypheptadine* (Periactin®)
 - An appetite stimulant in cats (and dogs)
 - Antiserotonin used for treating equine Cushing's disease and serotonin syndrome in small animals.

Benzodiazepines

- The benzodiazepines are effective appetite stimulants in cats (but not dogs) by induction of aminobutyric acid (GABA) and by central inhibition of the satiety center in the hypothalamus.
- Example : *Diazepam* (Valium[®]), *Oxazepam* (Serax[®])
 - Diazepam is the more effective appetite stimulant but also has a greater sedative effect than oxazepam.

Progestins

- ***Megestrol acetate*** (Ovaban[®], Megace[®]) is a synthetic progestin that has significant antiestrogen and glucocorticoid activity, which results in adrenal suppression.
- It is used to stimulate appetite and promote weight gain in anorectic cats and dogs.
- Contraindication : pregnant animals and in animals with uterine disease, diabetes mellitus, or mammary neoplasia.
- Side effects include behavior change, endometritis, and mammary enlargement.

Glucocorticoids

- Glucocorticoids increase gluconeogenesis and antagonize insulin resulting in hyperglycemia.
- Glucocorticoids such as *prednisone* (generic brands) stimulate steroid-induced euphoria, which in turn stimulates appetite.
- Side effects of glucocorticoids include polydipsia, polyuria, dull haircoat, weight gain, and behavioral changes.

5. Bile Acid Therapy For Gallstones

- Ursodiol, commonly known as **Ursodeoxycholic Acid (UCDA)** is used for dissolution of small cholesterol gallstones in patients with symptomatic gallbladder disease.
- Ursodiol decreases the cholesterol content of bile by reducing hepatic cholesterol secretion.
- UCDA has multiple drug actions including protection of hepatic cells from apoptosis, choleresis (induction of bile flow), suppression of hepatic synthesis and secretion of cholesterol, modulation of the immune system to reduce inflammation, and increasing the production of glutathione and metallothionein, which prevent oxidative damage.

6. Antioxidant

- **SAMe** (S-adenosyl Methionine)
 - SAMe is a normal metabolite in the hepatocytes and is important in the defense against free radicals.
 - Commercially, SAMe is available as a “nutraceutical” and is used as an adjunctive treatment for liver diseases in dogs and cats.
- **Silymarin** (silibinin) is the active component extracted from the fruit of milk thistle.
 - It has several pharmacological actions that may be useful in treating liver disease.
 - It inhibits lipid peroxidase and beta glucuronidase and the cytotoxic actions of tumor necrosis factor (TNF).
 - It is a strong free radical scavenger by induction of cellular SOD and may increase hepatic glutathione content and decrease hepatic collagen formation.

7. Antifoaming / Antiflatulent Agents

- ***Simethicone*** decreases the surface tension of gas bubbles thereby disperses and prevents gas pockets in the GI system.
 - Sometimes it is added to antacids.
- ***Poloxalene and polymerized methyl silicone***
 - Antifoaming agents that make the foam less stable, breaking it up to promote gas release through belching.
 - Used as bloat treatment in ruminants



Thanks!




Any questions?

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