

Chapter 10

Respiratory Pharmacology

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I. INTRODUCTION. The primary function of the respiratory system is gas exchange between the inspired air and the pulmonary artery blood. Because of the large surface area of the alveoli and exposure to the environment, this organ system is prone to antigen–allergy responses and infection. The defenses of the respiratory system include hypersecretion of mucus, sneezing and coughing reflexes, bronchoconstriction, and macrophage activation and inflammation. Pharmacology of the respiratory system centers around these defense mechanisms and can be simplified into seven categories: (1) elimination of excess secretions and membrane congestion, (2) bronchiole dilation when excessive constriction has occurred, (3) cough suppression when it is nonproductive and detrimental to the animal, (4) control of infection and inflammation, (5) decrease pulmonary hypertension, (6) stimulate the peripheral chemoreceptors and the central respiratory center, and (7) exogenous surfactant.

II. SECRETIONS. A thin layer of mucus coats the surface of all airways from the bronchioles to the larynx. This mucus is secreted by Clara cells, goblet cells, and submucosal bronchial glands located within the respiratory epithelium. Mucus protects airways by entrapping inhaled particles, humidifying inspired air, and maintaining mucosal hydration. Cilia, on the apical surface of respiratory epithelial cells, propel mucus out of smaller airways into the trachea and up to the larynx to be swallowed or expectorated. The mucociliary escalator is essential for the removal of airway secretions, pathogens, cellular debris, and inhaled particulate matter from the respiratory tract. Mucoprotein content of the mucus and transepithelial movement of water and ions determine the viscosity of normal mucus. Thick mucus can also be due to the presence of bacterial and neutrophil cellular debris. The cough reflex is very important for clearance of viscous mucus. Too much mucus narrows the lumen of bronchi restricting airflow and stimulates coughing. If coughing does not rid the airway of mucus, there are several pharmacologic options in addition to treating the underlying respiratory disease.

A. Increasing or facilitating the removal of excess, accumulated secretions. By decreasing the viscosity of these bronchial secretions, the normal action of the cilia and reflex coughing may be more effective.

1. Methods designed to loosen secretions by hydration of the mucus.
 - a. Nebulizer (aerosol) therapy with sterile or bacteriostatic water or saline produces a liquid particle suspension within a carrier gas (room air or oxygen) which, when inhaled, will add water to the airway mucus layer.
 - b. Always use physiotherapy in conjunction with nebulization.
 - (1) Improve tidal ventilation by mild-forced exercise after nebulization.
 - (2) Manually stimulating a cough reflex via chest wall coupage, vibration, or tracheal manipulation.
 - c. Efficacy is debatable.
 - d. Small volume jet or ultrasonic nebulizers produce particles of 0.5–3 microns, which are best for deposition in the lower respiratory tract.

- e. Large volume aerosol therapy may be beneficial in lobar pneumonia. Done with a bland aerosol (sterile saline) in an enclosed cage with a large ultrasonic nebulizer for 30–45 minutes 2–4 times per day.
- 2. *N*-Acetylcysteine (*N*-acetyl-L-cysteine) is a derivative of L-cysteine and acts as a mucolytic drug.
 - a. **N-Acetylcysteine** (NAC) breaks the disulfide bonds within the mucus molecules and decreases the viscosity.
 - b. NAC will not only alter the viscosity of normal mucus but also the thick mucus that results from the addition of bacterial and neutrophil cellular debris.
 - c. This drug is usually aerosolized and inhaled by the patient, but a powder form is available and can be formulated for oral use.
 - d. **Proven benefits from NAC have not been demonstrated in veterinary patients and aerosolized, it may cause airway irritation and bronchoconstriction.**
- 3. **Bromhexine HCl** is a frequently prescribed mucolytic.
 - a. Enhances the hydrolysis of acid mucopolysaccharides that significantly contributes to mucus viscosity.
 - b. Does not alter protein in the mucus, which originates from bacteria or neutrophil cellular debris.
 - c. May increase the concentration of certain antibiotics in the alveoli by altering the permeability of the alveolar/capillary membranes.

B. Expectorants theoretically make the bronchiole secretions less viscous but their efficacy is questionable.

- 1. **Potassium iodide** is an oral saline expectorant, which causes irritation to the gastric mucosa that in turn increases bronchiole secretion through a vagal reflex.
- 2. **Guaifenesin** is a guaiacol (wood tar) derivative that acts as an expectorant and increases airway particle clearance in humans.
 - a. Guaifenesin may stimulate the gastric mucosa and increase respiratory tract secretions via reflex.
 - b. The volume and viscosity of secretions does not appear to change.
 - c. This compound is primarily found in over-the-counter human cough preparations.

C. Decongestants shrink the nasal mucosa and allow air to pass more freely. Sinusitis or reverse sneezing are other indications for decongestants.

- 1. H_1 -antihistamines are commonly used for allergic-induced symptoms and chronic rhinitis in people but efficacy in animals is not documented. (See Chapter 3 for the pharmacology of H_1 -antihistamines.)
 - a. **Diphenhydramine**
 - b. **Dimenhydrinate**
 - c. **Chlorpheniramine**
 - d. **Hydroxyzine**
- 2. Sympathomimetic drugs (α -receptor agonists) may be given orally or topically as nasal sprays to avoid their systemic effects. However, nasal sprays are not well tolerated in animals. Their primary effect is to constrict the precapillary arterioles, reduce blood flow, and reduce the extracellular fluid in the nasal mucosa. Nasal discharge consequently will be reduced and resistance to airflow through the nasal cavity will decrease. (See Chapter 2 for information on the pharmacology of sympathomimetics.)
 - a. **Ephedrine**
 - b. **Pseudoephedrine**
 - c. **Phenylephrine**. This drug has been used to relieve anesthesia (recumbency)-induced nasal congestion and edema in horses. About 30 minutes before anesthetic recovery and removal of the endotracheal tube, phenylephrine is sprayed or squirted into the ventral meatus of each nostril with the external nares elevated.

III. **CONTROL OF INFECTION AND INFLAMMATION.** Antibiotic choice should ideally be based on culture and sensitivity or cytology with a Gram's stain.

A. Antibacterial drugs that have a good spectrum of activity. (See Chapter 15 for information on the pharmacology of antibacterial drugs.)

1. **Upper airway disease—Gram-positive spectrum is best.**
2. **Lower airway disease—Gram-negative spectrum is best.**
 - a. **Cephalosporins**
 - b. **Potentiated sulfonamides**
 - c. **Amoxicillin**
 - d. **Amoxicillin/clavulanate**
 - e. **Fluoroquinolones**
3. Aerosolized antibiotics may be helpful in selected cases of infectious tracheobronchitis.

B. Glucocorticoids

1. Corticosteroids are important for the treatment of antigen-induced inflammatory bronchial disease such as chronic obstructive pulmonary disease (heaves) in horses and feline bronchial disease (asthma), as well as chronic bronchitis in dogs. Glucocorticoids reduce mucus hypersecretion, bronchial mucosal thickening, and airway smooth muscle constriction. (See Chapter 12 for more information on glucocorticoids.)
 - a. Oral intermediate-acting steroids are preferred for ease of dosage adjustments.
 - (1) Prednisolone
 - (2) Prednisone
 - b. Fluticasone is an inhaled glucocorticoid that is being used more frequently in animals.
 - (1) It is available in a multidose inhaler (MDI) for human inhalation.
 - (2) An animal mask and spacer are needed for administration.
 - (3) It has 18× the affinity of dexamethasone for human glucocorticoid receptors.
 - (4) Only 30% of the administered dose reaches the airways of the lung.
 - (5) It may take 1–2 weeks of administration to see the maximum effects.
 - c. For other inhaled glucocorticoid aerosol drugs see Table 10-1.

C. Leukotriene receptor antagonists are a new type of therapy. Leukotrienes are potent bronchoconstrictors and trigger inflammatory responses such as edema formation.

1. These modulators of inflammation can be used instead of corticosteroids.
2. Drugs that antagonize leukotriene receptors are zafirlukast, zileuton, and montelukast.
3. Zafirlukast has been tested in cats with experimental asthma and found not to be beneficial.
4. Whether these drugs are of any use in respiratory therapy is yet to be determined.

D. Nonsteroidal anti-inflammatory drugs are seldom used to treat inflammatory respiratory diseases because they tend to inhibit cyclooxygenase more than lipooxygenase enzymes. Aspirin has been used in the treatment of thromboembolism in cases of heartworm disease.

E. Serotonin receptor inhibition may be beneficial for feline “asthma.” Cyproheptadine is the only drug in this category currently thought to be beneficial. (See Chapter 3 for information on cyproheptadine.)

F. Cyclosporine is an immunosuppressant drug but has been shown to be beneficial in experimental models of feline bronchial disease “asthma.”

G. Mast cell stabilizers are used in human medicine to treat allergic asthma. These cromones, cromoglycate and nedocromil, prevent the release of inflammatory

TABLE 10-1. Drugs Available as Metered Dose Inhalers (MDI)

Drug Class	Generic Name	Indication	Comments
Bronchodilator— β_2 -agonists	Albuterol	Immediate relief	Effect is short lived (<4 hours)
	Pirbuterol	Immediate relief	No animal data
	Salmeterol	Long-term (12-hour) control	Onset of action >1 hour
	Bitolterol	Immediate relief	No animal data
	Metaproterenol	Immediate relief	No animal data
	Terbutaline	Immediate relief	No animal data
	Pirbuterol	Immediate relief	No animal data
Anticholinergic agent	Ipratropium bromide	Additive bronchodilation with β_2 -agonists	No animal data
Anti-inflammatory corticosteroids	Fluticasone propionate	Long-term control of inflammation	Takes 10–14 days to reach peak effect
	Flunisolide	Long-term control of inflammation	No animal data
	Budesonide	Long-term control of inflammation	No animal data
	Beclomethasone dipropionate	Long-term control of inflammation	No animal data
	Triamcinolone	Long-term control of inflammation	No animal data
Mast cell stabilizer	Cromolyn sodium	Long-term control of inflammation	No animal data
	Nedocromil sodium	Long-term control of inflammation	No animal data

JAAHA 42:165–169, 2006, Use of inhaled medications to treat respiratory diseases in dogs and cats, by P. Padrid.

mediators from mast cells by inhibiting the influx of calcium. They are administered by inhalation and efficacy in animals is not documented. (See Chapter 3 for information on cromolyn sodium.)

IV. COUGH SUPPRESSION and normalization of other respiratory reflexes. Sneezing and reverse sneezing, coughing, and airway narrowing reflexes that result in laryngospasm and bronchospasm are reflexes that are part of the normal pulmonary defenses and should not be suppressed unless they are excessive or debilitating.

A. Coughing is the sudden and loud ejection of air from the lungs. It is a normal protective reflex that is necessary in the diseased animal. The sensory receptors for the reflex cough are subepithelial irritant or stretch receptors that are numerous in large airways and innervated by the vagus nerve. Foreign bodies or excessive amounts of mucus on the surface of the airways can mechanically deform a sensory receptor and stimulate the cough reflex. Inflammation of the airway, for example, a viral infection, may result in the receptors becoming hyperresponsive. During a cough, the intrapleural pressure rises dramatically against a closed glottis and as a result the intrathoracic airways are compressed. Air is expelled with considerable noise through a narrowed airway and material is dislodged from the walls of large airways. Coughing is usually a good way for the animal to clear mucus from large bronchi and the trachea, but not from the smaller distal bronchi and bronchioles. Coughing is frequently a beneficial reflex and should not be suppressed unless it is dry (nonproduction) or physically tiring to the

animal. Initial treatment of the coughing animal is aimed at eliminating the underlying cause and not suppressing the cough.

1. **Antitussives** decrease the severity and frequency of coughing.
 - a. Peripherally acting antitussives include anti-inflammatory drugs, mucolytics, and bronchodilators.
 - b. Central acting opioid and nonopioid drugs reduce the sensitivity of the cough center to afferent stimuli. The opioid cough suppressants may cause sedation, nausea, and constipation. (See Chapter 4 for more information about opioids.)
 - (1) **Codeine**—dogs and cats. One of the most effective with an antitussive effect that is much greater than its analgesic effect.
 - (2) **Hydrocodone**—commonly used in the dog. More potent antitussive than codeine.
 - (3) **Butorphanol**—100× more effective as an antitussive than codeine. Can be given orally or parenterally to dogs and cats. It has a short duration analgesia but longer sedative effect and minimal respiratory depression with a half-life of 1.7 hours.
 - (4) **Dextromethorphan** is a semisynthetic opioid that is found in many over-the-counter human cough preparations but its efficacy in animals is not documented.

V. BRONCHIAL DILATION is beneficial to decrease resistance to airflow when excessive constriction is present. The normal bronchi have a small amount of smooth muscle tone (constriction) due to the vagus nerve activity. The airway smooth muscle tone controls airway caliber and establishes a balance between resistance to airflow (constriction) and physiological dead space (dilation). Bronchial smooth muscle is regulated by local homeostatic mechanisms, plus neural and humoral control. Equine airways receive cholinergic, adrenergic, and nonadrenergic–noncholinergic inhibitory (iNANC) and excitatory (eNANC) innervation. Similar innervation has been observed in most domestic animal species. A variety of stimuli to the airway surface can initiate the bronchoconstrictive reflex arc, including mechanical (e.g., bronchoscopy, particulates) and chemical-autacoids (e.g., acid, histamine, and secretions) factors, pulmonary edema, pulmonary embolism, and pneumothorax.

A. Bronchodilators are common treatments for airway disease. The horse benefits the most from these drugs.

B. Parasympathetic system—provides innervation to the entire tracheobronchial tree. These cholinergic nerves arise in the brain stem and course through the vagus nerve to synapse in local ganglia within the walls of the alveoli. From these ganglia, post-ganglionic fibers travel to airway smooth muscle and submucosal glands. Ganglionic transmission is mediated by acetylcholine via neuronal nicotinic receptors, whereas smooth muscle contraction is mediated by acetylcholine via muscarinic receptors. M₃ muscarinic receptor subtypes mediate airway smooth muscle constriction, plus vasodilation and mucus secretion. Anticholinergic drugs will cause bronchodilation even in the normal healthy animal. (See Chapter 2 for more information about anticholinergic drugs).

1. **Atropine**—injectable
2. **Glycopyrrolate**—injectable
3. **Ipratropium**—aerosol by metered dose inhaler (MDI)
4. The parenterally administered anticholinergic drugs have significant side effects, including decreased GI peristalsis, dry mucous membranes, tachycardia, and urinary bladder relaxation. These side effects limit the chronic use of parenteral anticholinergic drugs and favor the aerosol administration of ipratropium directly to the lungs.

C. Adrenergic system—The sympathetic innervation plays an important role in the pathophysiology of airway diseases and treatment of bronchoconstriction. This system

includes not only the sympathetic innervation but also the adrenal medulla. Norepinephrine is the principal neurotransmitter of sympathetic nerves and epinephrine is secreted by the adrenal medulla and functions as a hormone. The sympathetic innervation of the bronchi is sparse when compared to the parasympathetic system. Response to the adrenergic nervous system primarily involves the activation of β_2 -adrenoreceptors that are distributed throughout the lung in all species. In vitro β_2 -agonists suppress the tone of airway smooth muscle both when the tone is of spontaneous origin and when induced by an exogenous spasmogen. Relaxation is mediated by the intracellular accumulation of cAMP, which inactivates myosin light chain kinase. There are α_1 - and α_2 -adrenergic receptors in the lung of several species. The α_1 -receptors mediate airway muscle contraction in the guinea pig, rabbit, and dog. The α_2 -receptors are inhibitory to cholinergic nerves and are responsible for a decrease in acetylcholine release. The selective β_2 -agonists are used clinically as bronchodilators but they are not 100% selective for β_2 -receptors and concurrently stimulate some β_1 -receptors. Since β_1 - and β_2 -receptors are distributed throughout the body, including the heart, overdosing these drugs may cause tachycardia, excitement, and sweating (horses). These drugs may transiently decrease systemic arterial blood pressure, which increases heart rate via the baroreceptor reflex. The β_2 -receptor stimulation in the respiratory tract also increases the ciliary beat frequency and mucociliary clearance rate. They have some anti-inflammatory activity and can decrease the release of mediators from mast cells. The use of metered dose inhalers (MDIs) in human medicine has led to more β_2 -agonist therapy and products available. These products can be used in animals with a spacer and mask.

1. Adrenergic agonists

- a. **Nonselective ($\alpha + \beta_1 + \beta_2$) agents** may be used for the acute treatment of bronchoconstriction.
 - (1) **Epinephrine**
 - (2) **Ephedrine**
 - (3) **Isoproterenol**
- b. **β_2 -Selective agonists** produce fewer undesirable α - and β_1 -effects.
 - (1) **Terbutaline**—orally or parenterally for severe bronchoconstriction in cats.
 - (2) **Isoetharine**—has been aerosolized and used in small animals.
 - (3) **Albuterol**—has been aerosolized and used in horses and small animals.
 - (a) It has a β_2/β_1 selectivity of 4.0.
 - (b) Reported to be beneficial for the treatment of hypoxemia in anesthetized horses.
 - (4) **Clenbuterol**
 - (a) Approved in the United States for use in horses with airway obstruction such as chronic obstructive pulmonary disease (heaves).
 - (b) β_2/β_1 Selectivity is 4.0.
 - (c) Administered orally.
 - (d) The $t_{1/2}$ in the horse is ~12 hours and the duration of effect is 6–8 hours.
 - (e) Also inhibits the release of proinflammatory cytokines IL1 β and tumor necrosis factor from macrophages.
 - (f) Adverse effects include muscle tremors, sweating, restlessness, urticaria, and tachycardia.
 - (5) Use these drugs cautiously in animals with concurrent diabetes, hyperthyroidism, hypertension, seizure disorders, or cardiac disease with arrhythmias.
 - (6) For other selective β_2 -agonistic aerosol drugs see Table 10-1.

D. Methylxanthines have been used for many years in veterinary medicine as a bronchodilator.

1. **Mechanism of action.** Methylxanthines are phosphodiesterase inhibitors, which induce bronchodilation by blocking the degradation of cAMP by phosphodiesterase in airway smooth muscle cells and inhibition of light chain myosin kinase. The increase of cAMP levels in mast cells inhibits the release of histamine and other autacoids, for example, leukotrienes which may reduce ongoing

bronchoconstriction. The increase of cAMP levels in the chromaffin cells of the adrenal medulla promotes the release of catecholamines which bronchodilate by stimulating noninnervated β_2 -receptors in the lung. The other benefits of the methylxanthines are increased mucociliary clearance, improvement in diaphragmatic contractility, decreased pulmonary artery pressure, increased CNS sensitivity to PaCO_2 , and stabilization of mast cells. In addition, methylxanthines are adenosine receptor antagonists. Adenosine receptors are coupled to $\text{G}_{i/o}$ protein, which mediate the decrease in cAMP formation by inhibiting adenylyl cyclase. Thus, adenosine receptor antagonists increase cAMP levels as well. Inhibition of adenosine receptors in the CNS may cause excitation, muscle tremors, and seizures. Increased cAMP levels in the myocardium can induce cardiac arrhythmias and the increased circulating catecholamine levels from the adrenal medulla can make the cardiac side effects worse by stimulating α - and β_1 -receptors.

2. Theophylline

a. Therapeutic uses. Theophylline is administered orally. It is used primarily to induce bronchodilation for the treatment of obstructive small airway diseases. It is advisable to use only theophylline products that are sustain-released and have suitable pharmacokinetics in animals. It is used often in patients with heart failure and/or pulmonary edema. Theophylline must be used cautiously because of its adverse effects (see below).

b. Pharmacokinetics

- (1) The GI absorption is $\sim 100\%$ after oral administration of a nonsustained-release product. The GI absorption of sustained release products yielded 30–80% bioavailability.
- (2) Theophylline is distributed widely in the body and penetrates the blood–brain barrier. The plasma binding activity of theophylline is low ($<14\%$). Because of low volume of distribution in cats (0.46 L/kg), obese feline patients should be dosed on a lean body weight basis.
- (3) It is metabolized in the liver to 3-methylxanthine and caffeine among other metabolites. 3-methylxanthine has weak bronchodilatory activity.
- (4) Theophylline and its metabolites are excreted via the kidneys; only 10% of a theophylline dose is excreted unchanged in urine.
- (5) The elimination $t_{1/2}$: ~ 8 hours in cats, ~ 6 hours in dogs, and 12–17 hours in horses.

c. Adverse effects

- (1) Side effects in dogs and cats include nausea and vomiting, restlessness, increased gastric acid secretion, diarrhea, polyphagia, polydipsia, and polyuria.
- (2) Side effects in horses include nervousness, excitability (auditory, tactile, and visual), tremors, diaphoresis, tachycardia, and ataxia.

d. Seizures or cardiac arrhythmias may occur in severe cases.

e. Beware of other drugs that may inhibit hepatic CYP450 enzymes (e.g., cimetidine and fluoroquinolones) because their concurrent administration may elevate plasma levels of theophylline.

E. Aerosol administration of drugs is new to veterinary medicine and their efficacy is yet to be documented, although numerous case reports support their use.

1. Optimal particle size for delivery to the trachea is 2–20 microns and to the distal airways is 0.5–5 microns.
2. The benefits of aerosol therapy are that of limiting systemic absorption of the drug and introducing the drug close to the site of the problem.
3. Used primarily to treat chronic obstructive airway disease of horses, lower airway disease in felines, chronic bronchitis in dogs, and kennel cough complex in young dogs.
4. Small animal and equine specific products for administering these agents using a facemask and spacer are commercially available.
5. Bronchodilators, an anticholinergic, corticosteroids, and some antibiotics (e.g., aminoglycosides) are the primary drugs administered by this route.

VI. Sildenafil decreases pulmonary hypertension. Pulmonary artery blood pressure may elevate due to an increase in vascular resistance. Pulmonary hypertension has been reported in dogs with many respiratory diseases with *Dirofilaria immitis* infestation being most common. The pathophysiologic reasons for pulmonary vascular hypertrophy and remodeling are not well understood in animals and probably multifactorial. Treatment of the underlying respiratory disease is important when pulmonary hypertension is discovered, but sildenafil, a phosphodiesterase type V inhibitor, has been administered orally to induce vasodilation and reduce pulmonary hypertension in dogs and humans.

A. Mechanism of action. Sildenafil decreases pulmonary arterial pressure by inducing potent relaxation of arterial smooth muscle. Cyclic GMP is a potent vascular smooth muscle relaxant; sildenafil increases cyclic GMP levels in vascular smooth muscle cells, which is due to its inhibition of degradation of cyclic GMP by phosphodiesterase V.

B. Pharmacokinetics

1. GI absorption after oral administration is nearly complete. T_{\max} is ≤ 60 minutes.
2. It is well distributed after GI absorption and 84% of the circulating level is bound by plasma proteins.
3. It is metabolized by CYP450 to many metabolites, which are excreted in the feces.
4. Its elimination $t_{1/2}$ in dogs is ~ 6 hours.

C. Adverse effects. These effects are not well defined in dogs. However, systemic hypotension can occur, particularly if combined with other medications that lower blood pressure (e.g., nitrates).

VII. Doxapram hydrochloride is an analeptic and a centrally acting **respiratory stimulant** that also increases the sensitivity of the peripheral chemoreceptors located in the carotid bodies. When injected IV to dogs, the respiratory rate and tidal volume (minute ventilation) increase.

A. Used to aid in the visual evaluation of laryngeal paralysis in the lightly anesthetized dog. The larynx normally abducts on inspiration because of the reflex contraction of laryngeal muscles. Dogs and cats with laryngeal paralysis, however, have reduced or no abduction on inspiration. Evaluation of laryngeal motion requires deep sedation, which unfortunately also reduces laryngeal movement making visual evaluation difficult and frequently incorrect. Injecting doxapram IV while observing the larynx of a deeply sedated dog significantly enhances laryngeal movement but has no effect on the paralyzed larynx making evaluation more reliable.

B. May stimulate respiratory effort in newborn animals but is not a substitute for endotracheal intubation and mechanical ventilation for resuscitation.

VIII. EXOGENOUS SURFACTANT can be administered directly into the respiratory tract of foals or calves that are born prematurely and show signs of respiratory distress. Surfactant is normally produced by the alveolar type II cells and is a complex mixture of phospholipids and protein. Surfactant is necessary in the alveoli to reduce the surface tension during inspiration and stabilizes alveoli during the resting phase after expiration. Animals born prematurely may lack surfactant production, and breathing requires an increase in effort and work. One treatment option is to inject exogenous surfactant into the lungs. Several products for human use are derived from animals.

- A.** Beractant is lipid extract of bovine lung with synthetic lipids.
- B.** Calfactant is a lipid extract of calf lung lavage fluid.

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Chapter 11

Drugs Acting on the Gastrointestinal Tract

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I. GENERAL CONSIDERATIONS

A. Gastrointestinal (GI) disease is a common clinical problem where signs of vomiting, diarrhea, and anorexia predominate. Rapid diagnosis is essential for symptomatic or specific therapies to be effective. A complete history and physical examination accompanied by appropriate laboratory tests aid in determining the etiology, location, and severity of the disease or disturbance. Endoscopy and mucosal biopsy are frequently required for diagnosis of chronic GI diseases, such as gastritis, malabsorptive syndromes, or idiopathic inflammatory bowel disease (IBD).

B. Nonspecific therapy

1. **Correction of fluid and electrolyte balance.** Persistent vomiting or watery small bowel diarrhea produces dehydration, electrolyte loss, and disturbances in acid–base balance that should be corrected by parenteral fluid therapy. With severe vomiting, there is variable loss of sodium, chloride, potassium, hydrogen, and bicarbonate that may cause metabolic acidosis. If the pylorus is obstructed, duodenal bicarbonate is retained while continued loss of gastric chloride, potassium, and hydrogen in the vomitus leads to metabolic alkalosis. Oral fluid and electrolyte replacement may suffice in animals having only mild acute diarrhea or if vomiting is infrequent or absent.
2. **Resting of the GI tract.** Best practice recommendations suggest that withholding food for 24–48 hours in acute GI disturbances is often effective in dogs and cats. Thereafter, feeding a bland diet often and in small amounts is generally indicated for 3–5 days at which time the original diet is gradually introduced. Potential benefits of dietary restriction include decreased gastric secretions, decreased amounts of osmotically active particles in the gut lumen, and the facilitation of mucosal healing (e.g., enterocyte regeneration).
3. **Dietary modification**
 - a. **Bland diet.** A bland, easily digested, low-fat diet such as boiled chicken or white fish or low-fat cottage cheese with rice should be offered after withholding food for 24–48 hours. Limiting dietary fat is important because unabsorbed fatty acids are hydroxylated by colonic bacteria into secretagogues which decrease mucosal absorption and promote increased fecal water loss.
 - b. **Lactose-free diet.** Milk products should be eliminated from the diet if there is lactose intolerance or a loss of mucosal brush border lactase from GI disturbances.
 - c. **Insoluble fiber.** Increased fiber absorbs water and normalizes intestinal transit in constipation and animals with colitis of diverse causes.
 - d. **Gluten-free diet.** Gluten-sensitive enteropathy has been reported to occur in Irish setter dogs. Clinical improvement is observed when affected animals are placed on a cereal-free diet.
4. **Provision of nutritional support.** Calories, proteins, and vitamins should be supplied to maintain a positive energy and protein balance. Enteral feeding is preferred over parenteral routes since this is most physiologic and prevents atrophy of the intestinal tract. Initial nutrient deficiencies are gauged by use of body condition scores (BCS), and specific nutrient requirements may be estimated by a variety of methods.
5. **Symptomatic therapies**
 - a. **Protectants and adsorbents.** Bismuth-subsalicylate and kaolin-pectin are often administered in acute diarrhea to coat and protect the intestinal mucosa, and because they may reduce intestinal secretions. See more below.

TABLE 11-1. Indications for Antibiotic Use in Gastrointestinal Diseases

Severe Mucosal Injury
– Parvovirus
– hemorrhagic gastroenteritis
– Salmon poisoning disease
Enteropathogenic Bacteria
– <i>Salmonella</i> , <i>Clostridia</i>
– <i>Campylobacter jejuni</i> , <i>E. coli</i>
– Cocci villus adherence
Antibiotic-responsive diarrhea (\pm small intestinal bacterial overgrowth)
Inflammatory Bowel Disease

Note: Antibiotics are uncommonly required in most cases of acute or chronic gastroenteritis. Their specific use is indicated in patients with severe mucosal disruption as evidenced by bloody diarrhea, and in animals diagnosed with specific enteropathogenic bacterial infections or other conditions. Indiscriminate use encourages antibiotic drug resistance and may prolong some types of infectious diarrhea (e.g., salmonellosis).

- b. Motility modifying drugs.** Opiates and opioids (loperamide, diphenoxylate) are used to decrease intestinal motility and secretions associated with acute diarrhea. Anticholinergics should be avoided since they can potentiate ileus. See more below.
- c. Antimicrobial therapy.** The routine use of antibiotics for treatment of acute or chronic GI disease is not recommended. Animals having severe mucosal injury (parvoviral enteritis) or infection with specific bacterial pathogens (*Campylobacter jejuni*) of the GI tract should receive antibiotics. Indiscriminate use of antimicrobials promotes bacterial drug resistance (Table 11-1).
- d. Probiotics.** These are live bacterial cultures, which promote beneficial microbial health to the host. The mechanism(s) of action are not fully known and their effects appear to be exquisitely host-specific. Preliminary clinical data supports their use as adjunctive therapy for both acute and chronic diarrhea (see below).
- e. Analgesics.** Indications include alleviation of visceral pain in animals having diverse causes for GI disease (equine colic, pancreatitis in companion animals). **Severe** visceral pain is alleviated by morphine or opioid receptor agonists that inhibit nociceptive reflexes at spinal and supraspinal sites within the CNS.
 - (1) Opiates** (see Chapter 4 for more information)
 - (a) Morphine** is used in dogs and cats, IM. Its duration of action is 6 hours in these species. High doses of morphine produce excitement in cats and horses and it is administered at 1/10 of the dose used in dogs (0.05–0.2 mg/kg in cats and horses; 0.5–2 mg/kg in dogs).
 - (b) Butorphanol** is administered IV to horses for the control of colic pain. Butorphanol is a partial agonist for μ -receptors and a full agonist for κ -receptors. Its duration of action is 1–2 hours.
 - (2) Nonsteroidal anti-inflammatory drugs (NSAIDs).** (see Chapter 7 for more information) Flunixin meglumine, or phenylbutazone are given IM or IV to horses for the control of colic pain. They inhibit prostaglandin synthesis by inhibiting the enzyme cyclooxygenase. Duration of action is 1–8 hours, depending on the cause and severity of pain.
 - (3) Sedatives.** Xylazine, detomidine, medetomidine, and romifidine are α_2 -adrenoreceptor agonists, which produce sedation and analgesia in equine colic. Their duration of action is 1–4 hours following IV or IM administration. (see Chapter 4 for more information).
 - (4) Spasmolytics.** *N*-butylscopolammonium bromide (Buscopan®) is an antispasmodic and anticholinergic drug used in horses for control of the abdominal pain of colic.

- (a) **Mechanism of action.** Bucospan® competitively inhibits parasympathetic activation of muscarinic receptors on intestinal smooth muscle cells.
- (b) **Therapeutic uses.** Bucospan® is administered IV to horses at a dose of 0.3 mg/kg for control of abdominal pain in colic and simple impactions.
- (c) **Pharmacokinetics.** The plasma $t_{1/2}$ of Bucospan® is 6 hours. It is eliminated equally via urine and feces.
- (d) **Adverse effects.** Transient tachycardia and decreased borborygmal sounds may be present for 30 minutes following administration. Bucospan® should not be used in impaction colics associated with ileus or in horses with glaucoma.

II. APPETITE STIMULANTS

A. Inappetence or anorexia is common with GI disease. Insufficient nutrient intake delays clinical recovery and may exacerbate the underlying disease. Note that the use of these drugs should be restricted to animals where nutritional intake is measured because of the inconsistent response to their use. Efficacy studies based on controlled clinical trials for use of any of the appetite stimulants is lacking. Enteral alimentation with liquid supplements is quite practical and very useful in small animals.

B. Palatable food. Small amounts of palatable food should be offered at frequent intervals. Warming the food may enhance appetite in carnivores. In general, commercial-derived and nutritionally complete diets should be fed. Homemade diets are quite appropriate for short-term use where the risk of specific deficiencies is minimized by the brief duration of feeding.

C. Benzodiazepines (see Chapter 4 for more information)

1. **Mechanism of action.** Benzodiazepines may suppress the satiety center in the hypothalamus via increased γ -aminobutyric acid (GABA) activity.
2. **Therapeutic uses.** Diazepam or oxazepam is used primarily in cats for short-term stimulation of appetite, although the effect is controversial. They are used less frequently in horses, dogs, and goats. Their effectiveness decreases after 2–3 treatments.
3. **Administration**
 - a. **Diazepam** is administered orally, IV (0.2 mg/kg), or IM once or twice a day.
 - b. **Oxazepam** is administered orally once a day at 2.5 mg/kg in cats.
4. **Adverse effects**
 - a. **Sedation and ataxia** are common and may be severe in weak or debilitated animals. Reduced dosage should be employed in these cases. Use cautiously in patients with preexisting renal or hepatic disease.

D. Cyproheptadine (see Chapter 3 for more information)

1. **Mechanism of action.** Cyproheptadine is a serotonin antagonist which suppresses the satiety center in the hypothalamus. It is also a histamine-1 (H_1) antagonist and is used as an antiasthmatic in humans.
2. **Therapeutic uses.** Cyproheptadine stimulates appetite in cats and in humans but not in dogs. It has been used experimentally in cats as an appetite stimulant.
3. **Adverse effects.** Sedation and dryness of mucous membranes are the most common side effects. Paradoxically, CNS excitement and marked aggressive behavior may occur in 20% of the cats given cyproheptadine.

E. Glucocorticoids

1. Glucocorticoids are frequently employed as appetite stimulants in sick or debilitated animals.

2. **Mechanism of action.** The mechanism by which glucocorticoids stimulate appetite is unknown. It may be due to euphoria—the increased feeling of well-being produced by glucocorticoids. This is, in part, a result of their anti-inflammatory action.
3. **Therapeutic uses.** Glucocorticoids are used as nonspecific, short-term therapy for appetite stimulation.
4. **Administration**
 - a. **Small animals.** Prednisolone or prednisone is given once every other day.
 - b. **Large animals.** Prednisolone or dexamethasone is given IM once a day.
5. **Adverse effects**
 - a. Glucocorticoids are immunosuppressive and may delay recovery from the underlying disease.
 - b. Decreased gastric mucus production occurs following glucocorticoid administration. Gastric ulcers may develop with high dose or long-term use or in animals where preexisting gastric mucosal disease is present.

III. ANTI-OBESITY DRUGS

A. General considerations. Obesity is an important medical condition with serious health implications. Obesity is characterized by the excessive accumulation and storage of fat in the body. Obesity can be defined as exceeding ideal body weight by 20% or more, or BCS of 8 or greater on a 9-point scale. Approximately 20–40% of dogs are considered overweight or obese. The most common cause for obesity is the overconsumption of food combined with inadequate exercise.

B. Dirlotapide (Slentrol®)

1. **Mechanism of action.** Dirlotapide is a selective microsomal triglyceride transfer protein (MTP) inhibitor that blocks the assembly and release of lipoprotein particles into the bloodstream (via the lymphatic system) in dogs. Its unique mechanism of action provides for potential weight loss by reducing appetite (which accounts for 90% of its clinical efficacy) and by decreasing fat absorption (accounting for about 10% of dirlotapide's activity).
2. **Therapeutic uses.** To reduce the obesity in dogs that has been associated with increased risk for development of musculoskeletal disease, hypertension, peripheral insulin antagonism, osteoarthritis, and cardiopulmonary diseases.
3. **Pharmacokinetics.** Dirlotapide acts locally in the gut to reduce appetite, increase fecal fat, and produce weight loss. Following oral administration, the mean serum $t_{1/2}$ is 2.8 hours with bioavailability ranging from 20–40%. There is no clinical effect following IV administration. The variable response between animals and decreasing response over time requires that the dose be regularly and individually titrated to effect. The drug undergoes enterohepatic circulation and is primarily excreted in the feces, with small amounts excreted in the bile and urine.
4. **Administration.** Dirlotapide is administered once daily as an oil-based solution formulated at a concentration of 5 mg/mL.
5. **Adverse effects.** The most commonly reported adverse effects include vomiting, diarrhea, anorexia, and lethargy.

IV. DRUGS THAT REDUCE ACID SECRETION AND PROVIDE MUCOSA PROTECTION

A. General considerations. Inhibitors of acid secretion and mucosal protectants are used in veterinary medicine to reduce the hydrochloric acid (HCl) content of the stomach and to promote mucosal healing in animals with ulcers and erosions. The parietal cell possesses receptors for histamine, gastrin, and acetylcholine (ACh)—each of which

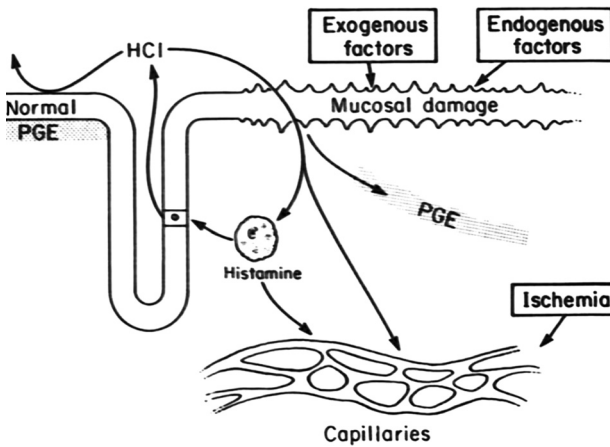


FIGURE 11-1. Overview of the etiopathogenesis of gastric ulceration. A common mechanism of H^+ back diffusion may occur as a consequence of either endogenous (infiltrative mucosal disease, renal or hepatic disease) or exogenous (NSAID use) disorders. Hydrogen ions present within mucosal tissues promote local vasculitis which causes ischemia and subsequent gastric mucosal disruption.

stimulates H^+ secretion into the lumen by the H^+/K^+ -ATPase pump located on the apical membrane. Disease conditions which disrupt the gastric mucosal barrier can lead to endoscopic lesions and clinical signs of GI ulceration or erosion. The fundamental lesion in these instances is the presence of an impaired mucosal barrier which permits the back diffusion of hydrogen ions which causes mucosal ischemia and subsequent damage (Figure 11-1).

B. Gastric secretory inhibitors

1. H_2 -antihistamines (see Chapter 3 for more information)

a. Mechanism of action. H_2 -antihistamines inactivate H_2 -receptors of parietal cells. Histamine-evoked gastric secretions are decreased; some (e.g., ranitidine) also have prokinetic activity mediated by their anticholinesterase activity. Ranitidine or famotidine are first-choice agents since they are safe, effective, and have less hepatic inhibition of microsomal metabolizing enzymes than cimetidine. Ranitidine is 3–13 times more potent as cimetidine. Famotidine has greater gastric inhibitory properties and can be given once daily.

b. Therapeutic uses

- (1) Ranitidine and famotidine are used to treat gastritis, gastric ulcer/erosions, reflux esophagitis, and gastrinomas (rare) in dogs and cats. Gastric HCl secretion is intermittent in carnivores rather than continuous as in humans; therefore, lower doses are effective. These drugs are also used to treat gastritis and gastric erosions in horses and foals.
- (2) H_2 -antihistamines are used to prevent acid hydrolysis of replacement pancreatic enzymes in exocrine pancreatic disease in dogs and cats.
- (3) Cimetidine or ranitidine are used to treat gastritis and gastric erosions in horses and foals.
- (4) **Ranitidine also stimulates gastric and colonic motility by inhibiting acetylcholinesterase activity.** See Section V for additional information

c. Pharmacokinetics. Ranitidine and famotidine are well absorbed orally and widely distributed in body tissues. Only 10–20% of drug is bound to plasma proteins. The plasma $t_{1/2}$ is 2–3 hours for ranitidine. Approximately $1/4$ to $1/2$ of the drug is metabolized by the liver. Metabolites and the parent drug are excreted by the kidneys.

d. Administration

- (1) **Ranitidine** is administered orally, IM, or IV every 12 hours.
- (2) **Famotidine** is administered orally or IV once daily.
- (3) Ranitidine may stimulate gastric and colonic motility via its prokinetic activity.

e. Adverse effects. Side effects are rare in animals at usual dosages. Use ranitidine cautiously in animals with impaired renal function. Liver enzyme alanine

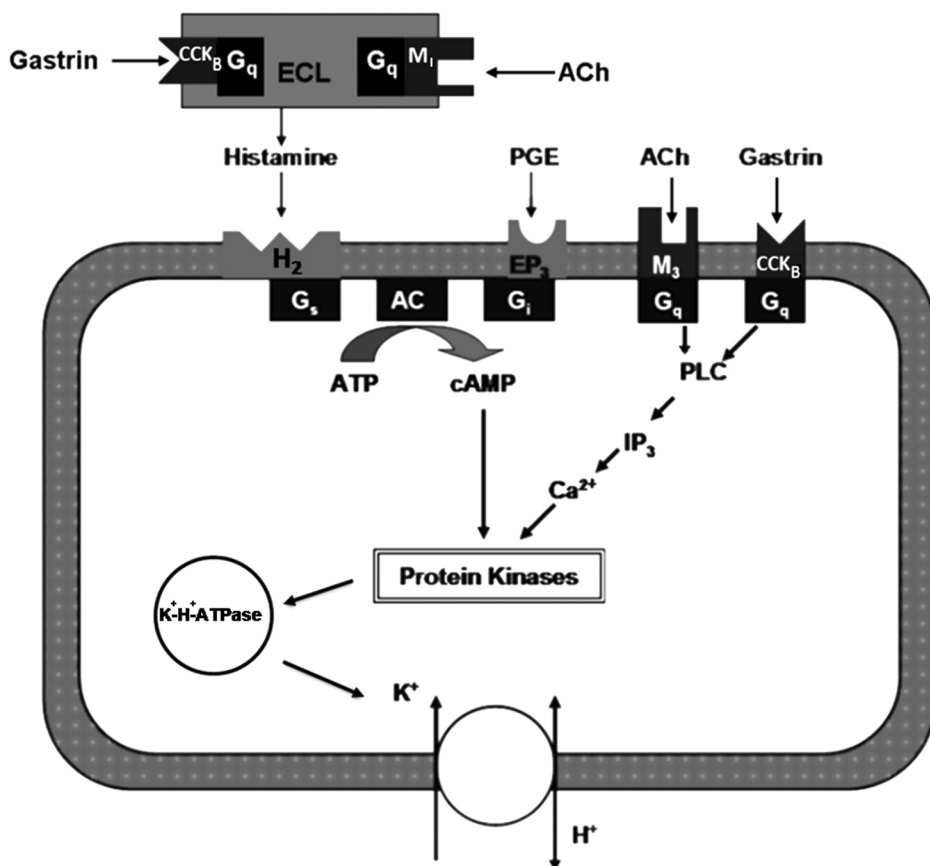


FIGURE 11-2. Regulation of gastric acid secretion in parietal cells. Acid secretion is increased by acetylcholine (ACh) and gastrin, which is mediated by M_3 -receptors and cholecystokinin B (CCK_B) receptors, respectively. Stimulation of both receptors increases cytosolic Ca^{2+} levels. Histamine, released from enterochromaffin-like (ECL) cells, increases acid secretion by activating H_2 -receptors, which increases cyclic AMP (cAMP) formation. Prostaglandin E decreases acid secretion by activating EP_3 receptors, which inhibits cAMP formation. Ca^{2+} and cAMP activate protein kinases, which translocate H^+ , K^+ -ATPase to the apical membrane of the cell to pump H^+ into lumen. Also, gastrin and ACh stimulate histamine release from ECL cells by activating CCK_B and M_1 -receptors. AC, adenyl cyclase; PLC, phospholipase C.

aminotransferase (ALT) concentrations should be occasionally monitored in animals receiving ranitidine in high doses for greater than 7 days. Some GI effects (anorexia, vomiting, and diarrhea) noted with famotidine. Famotidine has been associated with intravascular hemolysis when given IV to cats.

2. Proton pump inhibitors

- Mechanism of action** (Figure 11-2). Acid pump inhibitors inhibit the H^+/K^+ -ATPase on the luminal (secretory) membrane of parietal cells and thus reduce H^+ secretion. Binding to the enzyme is irreversible and restoration of acid secretion requires de novo synthesis of ATPase by the parietal cell. Omeprazole is the prototypical agent.
- Therapeutic uses.** Omeprazole is used in the treatment of gastritis, ulcer disease, and esophagitis in dogs, cats, and horses. It is also used in the prevention and treatment of NSAID-induced gastric erosions.
- Pharmacokinetics.** Omeprazole is absorbed orally and enters gastric parietal cells where it is protonated and trapped in the acidic intracellular fluid. The protonated drug is the active form and thus ATPase in nonacid-producing cells is not affected. Since the drug slowly accumulates in parietal cells with repeated

doses, pharmacologic action is not correlated with plasma $t_{1/2}$. Omeprazole is metabolized by hepatic microsomal enzymes and excreted by the kidney.

- d. **Administration.** Omeprazole is administered orally once a day.
- e. **Adverse effects.** Omeprazole, like cimetidine, inhibits hepatic microsomal (cytochrome P-450) metabolism and may prolong the action of concurrently administered drugs that are metabolized by this system (phase 1 reactions) such as phenytoin or phenobarbital. Use cautiously in animals with preexisting hepatopathy.

C. Mucosal cytoprotectants

1. **Pharmacologic protection of the gastric mucosa** can be enhanced by administration of a prostaglandin E_1 analog (Misoprostol) or by promoting direct cytoprotection of denuded mucosa (sucralfate).
2. **Misoprostol**
 - a. **Mechanism of action.** Misoprostol has two functions that make it a useful protective agent. It directly inhibits gastric acid secretion by parietal cells and it facilitates PGE-mediated mucosal defenses and healing in response to acid-related injuries.
 - b. **Therapeutic uses.** Misoprostol is used to treat gastric ulceration when caused or aggravated by NSAIDs drugs.
 - c. **Pharmacokinetics.** Approximately 90% of the drug is readily absorbed from the GI tract where a significant amount is metabolized via a first-pass hepatic effect. The presence of food and antacids will delay drug absorption. Metabolites and small amounts of parent drug are excreted in urine. The duration of action is 3–6 hours.
 - d. **Administration.** Misoprostol is given orally three times daily.
 - e. **Adverse effects.** Adverse GI signs include diarrhea, vomiting, and abdominal pain. It should not be given to pregnant animals as it will promote uterine contractions.
3. **Sucralfate**
 - a. **Mechanism of action.** Sucralfate is a sucrose sulfate-aluminum hydroxide complex which polymerizes to a viscous gel at pH < 4 and coats ulcer craters. Sulfate groups bind to proteins in ulcerated tissue and protect ulcers from acid and pepsin.
 - b. **Therapeutic uses.** Sucralfate provides locally acting treatment for GI ulceration. It also provides cytoprotection when used as a slurry in animals having mucosal disruption of the esophagus (esophagitis).
 - c. **Pharmacokinetics.** Only 3–5% of an oral dose of sucralfate is absorbed where it is then excreted in the urine unchanged. The remainder of the drug is converted into sucrose sulfate in the gut by reacting with HCl. The duration of action persists for up to 6 hours after oral dosing.
 - d. **Route of administration.** Sucralfate is given orally 2–3 times daily depending on the severity of mucosal disruption.
 - e. **Adverse effects.** Sucralfate may impair absorption of other oral medications so it is advised to stagger administration with other drugs by 2 hours or more.

V. PROKINETIC DRUGS

- A. **General considerations.** GI motility disorders result from diseases that, either directly or indirectly, alter normal GI functions (e.g., storage of ingesta, mixing and dispersion of food, and timely propulsion of luminal contents aborally). Briefly, the causes for GI transit disorders are diverse but include both structural (mechanical obstruction) and functional (defective propulsion associated with mucosal inflammation) diseases. Prokinetic drugs act to increase GI motility by stimulating smooth muscle contractions.

B. Specific drugs**1. Cisapride**

- a. **Mechanism of action.** Cisapride enhances the release of acetylcholine at the myenteric plexus, but does not induce nicotinic or muscarinic receptor stimulation. Cisapride blocks dopaminergic receptors to a lesser extent than does metoclopramide. This drug is no longer commercially available and must be obtained from a compounding pharmacy.
- b. **Therapeutic uses.** Cisapride stimulates GI motility from the lower esophageal sphincter (LES) to the descending colon. Proposed uses for cisapride in small animals include gastric/intestinal stasis, reflux esophagitis, and constipation/megacolon in cats.
- c. **Pharmacokinetics.** Information only in humans is available: Cisapride is rapidly absorbed following oral administration with an absolute bioavailability of 35–40%. The drug is highly bound to plasma proteins and is extensively distributed throughout the body. Its elimination $t_{1/2}$ is 8–10 hours.
- d. **Administration.** The drug is administered orally at a range of 0.1–0.5 mg/kg PO q8 hours.
- e. **Adverse effects.** The adverse effect profile is ongoing but the primary adverse effects are GI in origin, including diarrhea and abdominal pain.

2. Metoclopramide

- a. Metoclopramide stimulates motility of the proximal GI tract, especially the LES and stomach. See Section IX for more detailed information.
- b. Metoclopramide exerts its effects through antagonism of dopaminergic D_2 receptors and agonism of serotonergic 5-HT₄ receptors.
- c. Clinically useful in cases of reflux esophagitis and gastric stasis or hypomotility.

3. Ranitidine

- a. In addition to its antisecretory activity, ranitidine stimulates GI motility by inhibiting acetylcholinesterase activity. See gastric antisecretory drugs for more detailed information.
- b. As a parasympathetic potentiating agent, ranitidine stimulates gastric emptying and small intestinal and colonic motility. Its actions appear to be greatest in stimulating gastric motility.

4. Erythromycin

- a. The effect of erythromycin on GI motility most closely mimics that of the GI hormone, motilin. It stimulates motility by means of direct motilin-receptor activation (cats) and indirect cholinergic and neurokinin activation (in dogs).
- b. Sub-antimicrobial doses (0.5–1.0 mg/kg) are orally administered to induce prokinetic activity in dogs and cats. GI motility is stimulated most robustly in the proximal GI tract.
- c. Erythromycin is used clinically to increase gastric emptying and for the therapy of reflux esophagitis.

VI. DIGESTANTS**A. Pancrelipase (Pancreatin)**

1. **Pancrelipase** consists of pancreatic enzymes, including lipase, amylase, and protease, and is derived from porcine pancreas.
2. **Pancrelipase** powder preparations are mixed with food to treat exocrine pancreatic insufficiency in dogs and cats.
3. Enteric coated tablets have limited efficacy and are not recommended because of delayed gastric emptying of these preparations.
4. The maintenance dosage for the powdered preparation is 1 tsp/meal for dogs that weigh 20–30 kg.

An overview of hepatic therapeutic considerations

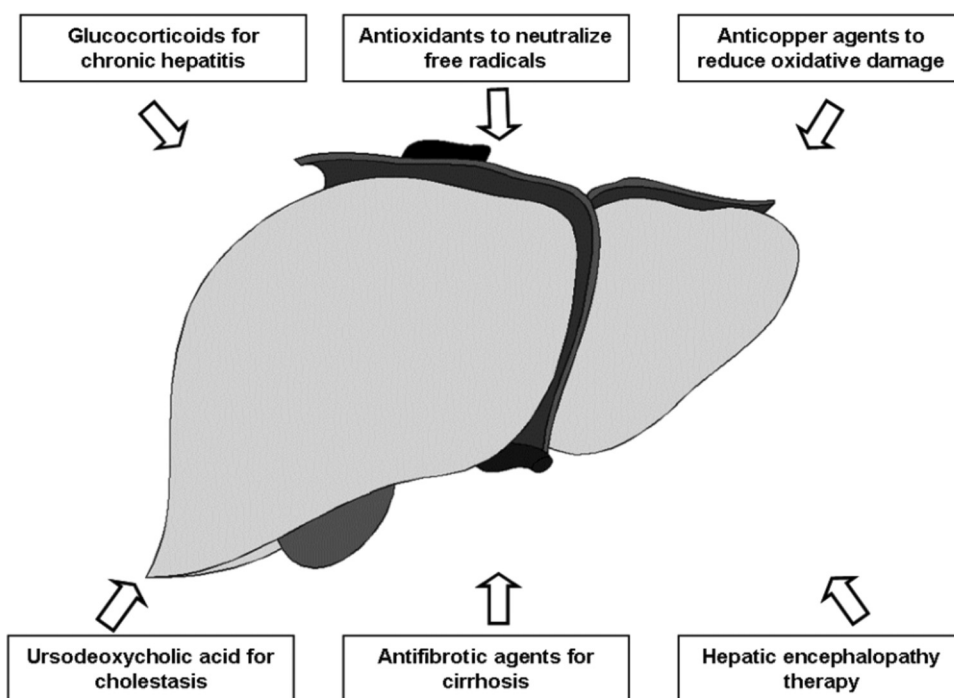


FIGURE 11-3. Overview of medical therapy for canine and feline hepatopathy. Therapy may be symptomatic and/or specific as dictated by the histopathologic findings obtained through the performance of hepatic biopsy. Note that both dietary and pharmacotherapy are utilized in dogs and cats to reduce hepatic workload, to treat signs of hepatic encephalopathy, and to facilitate repair of injured liver parenchyma.

VII. DRUGS USED FOR TREATMENT OF LIVER DISEASES

A. General considerations. A variety of diverse and clinically useful medications are used to treat dogs and cats with liver diseases. Unfortunately, few controlled clinical trials exist that provide critical evaluation of their effectiveness. Drug therapy is one important arm in treating hepatobiliary diseases along with dietary therapy. Symptomatic and specific therapies for liver disease are diverse but generally include both dietary and pharmacotherapy to induce patient remission (Figure 11-3).

B. Glucocorticoids (Prednisone and Prednisolone) (see Chapter 12 for more information)

1. Steroid therapy is the most commonly used therapy for chronic hepatitis in dogs. Prednisone must be metabolized into prednisolone by the liver so it is best to use prednisolone in case of liver disease.
2. Prednisolone is the treatment of first choice for idiopathic chronic hepatitis.
3. Corticosteroids have anti-inflammatory effects but also antifibrotic and choleretic effects. Their principle indication is immunomodulation.
4. Glucocorticoids are contraindicated for infectious diseases of the liver and biliary system.

C. Ursodeoxycholic acid

1. Ursodeoxycholic acid (UDCA), ursodiol, is one of the natural bile acids in the enterohepatic circulation. Ursodiol is an oral medication administered to dogs and cats at a dosage of 15 mg/kg once daily.
2. 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.
3. Although generally well tolerated, UCDA is contraindicated in patients having extrahepatic biliary obstruction.

D. Antioxidants

1. Oxidative stress and damage caused by free oxygen radicals may be a primary or contributory cause of liver disease.
2. The normal host cellular defense mechanisms against oxidative damage include superoxide dismutase (SOD), catalase, and glutathione (GSH) peroxidase.
3. The main antioxidants are vitamins C and E, silymarin, and *S*-adenosyl-L-methionine (SAME).
4. 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. Dosage varies as per species and by body weight but it is given once daily.
5. 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.

E. Antifibrotic drugs

1. Fibrosis may follow a variety of chronic liver insults and result in cirrhosis and incapacity of the liver to regenerate.
2. Increased lipid peroxidation of hepatocytes (e.g., hepatocellular damage) activates the mesenchymal hepatic stellate cells to produce fibrinogenic substances and extracellular collagen matrix.
3. Colchicine is the only drug used specifically to stop and reduce fibrosis. It is thought to act via stimulation of collagenase activity. Use of this drug is not strongly advocated since clinical studies have not been performed which prove its efficacy.

F. Anticopper medications

1. Chronic copper accumulation may cause oxidative damage to the liver because of the increased intracellular copper concentrations.
2. Hereditary copper toxicosis occurs in Bedlington terriers, and copper accumulation may also occur secondary to diseases in which cholestasis is a prominent feature.
3. Chelating drugs, such as D-penicillamine, can actively bind free extracellular copper and facilitate its excretion in the urine. D-penicillamine is administered orally twice daily with meals.
4. Chelators bind free copper actively and are an effective way to quickly remove increased intracellular copper that causes hepatic damage.
5. Zinc gluconate or acetate is another anti-copper medication for oral use (10 mg elemental zinc/kg twice daily). In the intestinal tract, zinc induces metallothioneine in the enterocytes. This protein binds copper which prevents its absorption, and it is sequestered within senescent enterocytes and shed into the intestinal lumen.

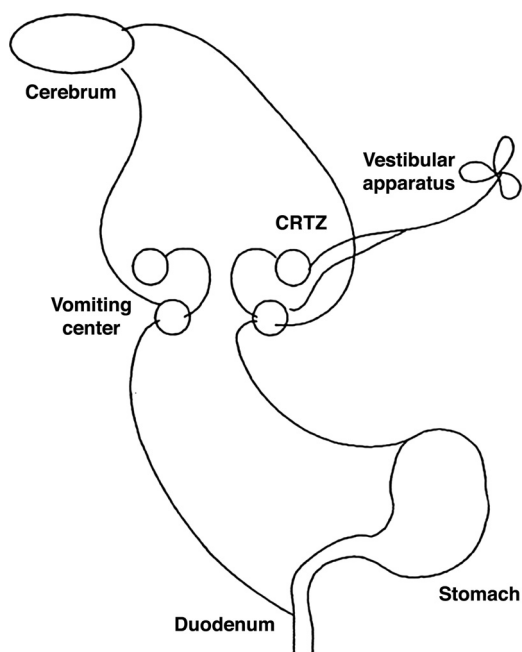


FIGURE 11-4. Simplified schematic showing major input pathways into the vomiting center. While central (CNS disease) and vestibular (motion sickness, vestibular disease) causes for vomiting occur in dogs and cats, they are relatively uncommon. More common causes for vomiting include the stimulation of the CRTZ via blood-borne toxins (uremia, hyperbilirubinemia) or drugs (digitalis, chemotherapy), and abdominal parenchymal disorders that promote irritation, distension, or inflammation of these organs.

G. Drugs to treat hepatic encephalopathy

1. Hepatic encephalopathy (HE) may occur as a consequence of both congenital and acquired hepatic diseases. Ammonia and aromatic amino acids are the two main factors contributing to HE.
2. Portosystemic encephalopathy is the most common cause and is treated with both dietary modification (reduced protein intake of aromatic amino acids) and pharmacologic agents.
3. Lactulose and soluble fibers will reduce ammonia metabolism, and thereby reduce clinical signs. These agents are metabolized by the colonic bacterial flora to produce acids that reduce the pH of the colonic contents. Ammonia is then present in the ionic form that is not absorbed and thus is excreted in the feces.
4. Lactulose is a disaccharide molecule that is metabolized by the resident flora into many osmotically active particles that attract water into the feces. The best guideline for use of lactulose in the management of HE is to give just enough (twice daily) to produce a soft stool.
5. Metronidazole is an antibiotic used as adjuvant therapy in HE. Metronidazole has efficacy against most obligate anaerobes, some of which are urease-producers, which may contribute to ammonia production and exacerbation of HE. Metronidazole is administered orally at 10–20 mg/kg twice daily in dogs and cats.

VIII. EMETICS

A. General considerations

1. The vomiting center in the medulla is activated by vagal and sympathetic afferents from the GI tract, dopaminergic input from the chemoreceptor trigger zone (CRTZ), and cholinergic and histaminergic afferents from the vestibular apparatus (Figure 11-4).
2. The vomiting reflex is developed in carnivores, primates, and swine. Horses, ruminants, rodents, rabbits, and guinea pigs do not possess this protective reflex.

3. Emetics may be used in conscious dogs and cats for elimination of noncorrosive poisons or prior to induction of general anesthesia to minimize gastroesophageal reflux.
4. Emetics generally remove less than 80% of stomach contents.

B. Central acting emetics

1. Apomorphine HCl

- a. Apomorphine is a synthetic derivative of morphine which stimulates dopaminergic receptors in the CRTZ to induce vomiting in dogs. It is administered parenterally because oral absorption is slow. It is conjugated in the liver and excreted in urine.
 - b. IV administration of a low dose is the preferred route. Onset of vomiting occurs in 1 minute, with a duration of 3–5 minutes. Apomorphine is also effective IM, SQ, or via conjunctival drops. Apomorphine administration should not be repeated because the vomiting center is depressed after the initial CRTZ stimulation.
 - c. Apomorphine produces excitement in cats and is not effective in swine.
- #### **2. Xylazine (see Chapter 4 for more information)**
- a. Xylazine is an α_2 -adrenoreceptor agonist, which induces vomiting in cats following IV or IM administration.
 - b. Onset of vomiting occurs in 2–5 minutes and may be followed by mild sedation for 30–90 minutes.

C. Peripheral acting emetics. Peripheral acting emetics stimulate sympathetic and vagal afferent receptors in pharynx and stomach to induce vomiting. They may be useful as household emetics if the owner has observed ingestion of poison by a pet. They are administered orally as a *single* dose that should not be repeated even if vomiting fails to occur.

- a. **Sodium chloride** is administered as crystals of table salt (1 tsp into pharynx). It is the most effective household emetic in dogs.
- b. **Syrup of Ipecac** contains emetine alkaloid and is the recommended household emetic for children. It is less reliable in dogs and cats but may induce vomiting in 15–30 minutes.
- c. **Copper sulfate** (1%), **zinc sulfate** (1%), or **hydrogen peroxide** (3%) solutions may produce emesis but the response is variable and they are seldomly used now.

IX. ANTIEMETICS

A. General considerations

1. General causes for vomiting include the following:
 - a. Stimulation of the vomiting center via vagal and sympathetic afferents from the GI tract in response to irritation, distension, or inflammation. Common clinical examples would include vomiting associated with enteritis, pancreatitis, or intestinal foreign body.
 - b. Stimulation of the vomiting center via vestibular afferents from the eighth cranial nerve in response to labyrinthine disease or motion sickness. This is an uncommon cause for vomiting but it might be seen in animals with motion sickness or vestibular diseases.
 - c. Stimulation of the vomiting center via inflammation, edema, or tumors of the CNS.
 - d. Stimulation of the CRTZ by drugs, bacterial endotoxins, or toxic endogenous metabolites such as urea or bilirubin.
2. Prolonged vomiting may lead to electrolyte and acid-base imbalances and dehydration. Diagnosis and treatment of the primary cause should precede administration of antiemetic drugs.

3. Specific indications for use of antiemetic agents include (1) animals with persistent vomiting in which fluid and electrolyte balance cannot be maintained and (2) abolishing the vomiting “cycle” such that animals can get sufficient rest to recover from their illness.
4. Indiscriminate use of antiemetics in vomiting animals is *not* recommended since this may mask the presence of more serious disease.

B. Antidopaminergic agents

1. Phenothiazines (see Chapter 4 for more information)

- a. **Mechanism of action.** The phenothiazine tranquilizers exert their antiemetic action by blockade of dopamine (D_2)-receptors in the CRTZ and, at higher doses, the vomiting center. Although they are broad-spectrum antiemetics, they tend to be less effective in vomiting arising from severe inflammation of the GI tract or the inner ear. Blockade of α -adrenoreceptors occurs in addition to dopamine receptor blockade. Phenothiazines also have weak anticholinergic and antihistaminic actions.
- b. **Pharmacokinetics.** Phenothiazines are well absorbed orally although there is significant first-pass metabolism. Distribution is wide. The drugs are metabolized by the liver primarily to glucuronide or sulfate conjugates and excreted by the kidney.
- c. **Administration.** Acepromazine, chlorpromazine, promazine, or prochlorperazine are administered orally or IM every 6 hours to prevent vomiting in dogs and cats.
- d. **Adverse effects.** Hypotension and bradycardia due to α -adrenergic blockade are the most serious side effects of the phenothiazines and are more likely to occur in dehydrated animals. Hypotensive reactions should be treated with α -adrenergic agonists such as phenylephrine. Epinephrine should not be used because of the possibility of epinephrine reversal. Sedation may occur but is usually mild at the doses used for antiemesis.

2. Metoclopramide

- a. **Mechanism of action.** Metoclopramide has both central and peripheral antiemetic actions. Its central action is due to blockade of dopamine receptors in the CRTZ and, at higher doses, inhibition of serotonin receptors in the CRTZ. Its peripheral action is due to stimulation of the motility of the stomach and duodenum via increased smooth muscle sensitivity to acetylcholine. This prevents the gastric atony required for the vomiting reflex and ejection of gastric contents.
- b. **Pharmacokinetics.** Oral absorption is rapid with peak plasma levels within two hours. The bioavailability of oral doses is 50–70% due to first pass metabolism. Distribution is wide and includes the CNS. Unchanged drug (25%) and conjugated metabolites (75%) are excreted in the urine. The plasma $t_{1/2}$ is 90 minutes in the dog.
- c. **Administration.** Metoclopramide (Reglan®) is given orally, SC, or IM every 8 hours or by constant rate IV infusion to control severe vomiting in dogs and cats. It is also administered 30 minutes prior to feeding in the treatment of disorders of gastric motility and esophageal reflux in dogs, cats, and foals.
- d. **Adverse effects.** Metoclopramide is contraindicated in animals with gastric outlet obstruction since stimulation of gastric motility may predispose to hemorrhage or perforation. Behavioral changes including excitement or disorientation may be observed in dogs and cats, although the incidence is low.

3. Butyrophenones

- a. Droperidol and haloperidol are neuroleptic drugs which are also central-acting antiemetics. They act by blockade of dopaminergic neurons in the CRTZ via their affinity for D_2 -receptors. Pharmacokinetic data for animals is lacking. The elimination $t_{1/2}$ in humans is 20–40 hours. They thus have a long duration of action—2–4 days.
- b. Their clinical use in veterinary medicine has been limited but they may be useful in vomiting associated with cancer chemotherapy.

- c. **Administration.** The butyrophenones are given orally or IM every 2–4 days.
- d. **Adverse effects.** Butyrophenones may produce mild sedation and tranquilization.

C. Antihistaminic agents (see Chapter 3 for more information)

1. **Mechanism of action.** Antihistaminic agents block histaminergic and cholinergic afferents from the vestibular organs to the vomiting center. They are useful in the prevention of motion sickness in dogs.
2. **Pharmacokinetics.** Antihistamines are well absorbed orally. Their physiological disposition has not been studied in animals.
3. **Administration.** Dimenhydrinate, diphenhydramine, or promethazine are administered orally every 8 hours.
4. **Adverse effects.** Sedation may be observed as a side effect but is much less prominent in animals than in humans.

D. Anticholinergic agents

1. **Mechanism of action.** Anticholinergic drugs block cholinergic afferents from the GI tract to the vomiting center. Although they are generally less active than other antiemetics when used alone, they may be effective when combined with phenothiazines in the control of emesis arising from severe gastroenteritis. An example of this combination is isopropamide + prochlorperazine = Darbazine.[®] Note that controlled clinical studies attesting to the clinical efficacy of this product have not been performed.
2. **Administration.** Aminopentamide, propantheline, or isopropamide are administered orally, IM, or SC every 8–12 hours for the symptomatic control of vomiting and diarrhea in dogs and cats.
3. **Pharmacokinetics.** **Pharmacokinetics of propantheline are stated in Chapter 2 VI C. Pharmacokinetics of aminopentamide and isopropamide are not available for animals.**
4. **Adverse effects.** Anticholinergics are contraindicated in patients with glaucoma. Dryness of the mouth (xerostomia) and/or eyes (xerophthalmia), tachycardia, and constipation may occur.

E. Antiserotonergic agents ondansetron and dolasetron

1. **Mechanism of action.** Ondansetron and dolasetron specifically inhibit serotonin type 3 (5-HT₃) receptors located peripherally on vagal nerve terminals and centrally in the CRTZ. Inhibition of 5-HT₃ receptors blocks neurotransmission by closing sodium channels. Antineoplastic drugs and radiation therapy damage GI mucosa which results in the release of serotonin and emesis.
2. **Therapeutic uses.** Ondansetron or dolasetron are used in dogs undergoing cancer chemotherapy or radiation therapy to control emesis.
3. **Pharmacokinetics.** Animal data are not available. In humans, ondansetron is well absorbed with peak plasma levels in 2 hours and an elimination $t_{1/2}$ of 3–4 hours. Ondansetron is extensively metabolized by the liver. Dolasetron is converted to its active metabolite, hydrolasetron, by plasma carbonyl reductase. Approximately two-third is subsequently metabolized by the liver and one-third is excreted unchanged in the urine. The antiemetic effect of both drugs persists after their disappearance from the circulation suggesting continued binding at the receptor level.
4. **Administration.** Ondansetron is administered orally or IV once or twice a day. Dolasetron is administered IV once a day.
5. **Adverse effects.** Side effects are rare. Constipation, extrapyramidal symptoms, hypotension, and cardiac arrhythmias may occur.

F. Miscellaneous antiemetics

1. Alimentary demulcents/adsorbents such as kaolin, pectin, or bismuth salts may reduce vomiting in mild gastritis.

2. Gastric antacids such as magnesium hydroxide, magnesium silicate, aluminum hydroxide, or aluminum silicates may reduce vomiting in cases of gastric hyperacidity.
3. **NK₁ receptor antagonist maropitant (Cerenia®)**
 - a. A new antiemetic agent for use in dogs with ongoing emesis is a neurokinin (NK) receptor antagonist which serves as a ligand for substance P (NK₁) receptors located in the vomiting center. Maropitant blocks neurotransmission of afferent emetic signals from the GI tract and other abdominal organs.
 - b. Maropitant is administered to dogs once daily SC at 1 mg/kg/day for up to 5 days for prevention and treatment of acute vomiting. The oral tablets can be used to prevent motion sickness at 8 mg/kg/day for up to 2 days.
 - c. Pilot data suggest that maropitant is clinically superior to metoclopramide in the control of general emesis in dogs. Additional studies are needed to confirm these earlier observations.
 - d. **Pharmacokinetics**
 - (1) The oral bioavailability of maropitant is 37%. T_{\max} is ~2 hours. The plasma protein binding of maropitant in dogs is >99%.
 - (2) Maropitant is metabolized by cytochrome P450 enzymes in the liver.
 - (3) Renal clearance is a minor route of elimination with <1% of an 8-mg/kg oral dose appearing in the urine as parent drug or metabolite. The data suggest that GI is the major route of elimination for maropitant, when given orally.
 - (4) The elimination $t_{1/2}$ is ~4 hours.

X. LAXATIVES

A. General considerations. Laxatives promote evacuation of the bowel through stimulation of fluid and electrolyte transport and increases in propulsive motility. Specific indications for the use of laxatives in dogs and cats are

1. To relieve severe constipation or obstipation which is causing fecal impaction.
2. To enhance intestinal motility that eliminates poisons from the GI tract.
3. To evacuate the large bowel prior to surgery, select radiographic procedures (e.g., excretory urography), or lower GI (e.g., colonoscopy) endoscopic procedures.

B. Hyperosmotic laxatives

1. **Mechanism of action.** Hyperosmotic laxatives are nonabsorbable or poorly absorbable salts or polymers which osmotically retain water in the intestinal lumen. They have a rapid onset of action which begins in the small intestine.
2. **Lactulose** is the most effective agent in this group. The organic acids produced from lactulose fermentation stimulate colonic fluid secretion and propulsive motility. Lactulose is administered at a dose of 0.5 mL/kg body weight two or three times daily.
3. **Polyethylene glycol.** Electrolyte solutions (Golytely®, Colyte®) are isotonic mixtures of polyethylene glycol, sodium sulfate, sodium bicarbonate, sodium chloride, and potassium chloride. They are administered orally prior to colonoscopy in dogs. Anecdotal reports suggest that they are safe to use in cats.
4. **Magnesium sulfate** (Epsom salts) or magnesium hydroxide (Milk of Magnesia®) are administered orally. They should not be used in the presence of renal disease since 20% of the magnesium ions are normally absorbed and are excreted by the kidney. CNS depression may result from elevated levels of plasma magnesium ions.

C. Bulk laxatives

1. **Mechanism of action.** Bulk laxatives comprise poorly digestible polysaccharides which absorb water and increase fecal bulk which stimulates large bowel

peristalsis. These products also reduce tenesmus associated with large bowel dysfunction (e.g., colitis, fiber-responsive diarrhea). Most of these products are dietary fiber supplements. Since they act in the large bowel, their onset of action is slow—normally 1–3 days.

2. Methylcellulose, wheat bran, or psyllium are added to the diet. Dietary fiber is preferable because it is well tolerated, more effective, and more physiologic than other laxatives.
3. Their use is indicated in dogs and cats having mild constipation or as adjunctive therapy to reduce clinical signs of colitis.

D. Lubricants and surfactants

1. Mineral oil (liquid petrolatum) and white petrolatum lubricate and soften fecal mass. These agents should only be given via rectal administration to minimize the risk of aspiration if given orally.
2. Docusate is an anionic surfactant which hydrates and softens stools by an emulsifying action.

E. Emollient laxatives

1. Emollient laxatives are anionic detergents that increase the miscibility of water and lipid in digesta, thus enhancing lipid absorption and impairing water absorption. Dioctyl sodium sulfosuccinate and dioctyl calcium sulfosuccinate are two common emollients available in oral formulations.
2. The dosage for both emollient laxatives is 50 mg orally given once daily in the dog and cat.
3. The clinical efficacy of either product in treating canine or feline constipation has not been proven in controlled clinical trials.

F. Irritant laxatives

1. **Mechanism of action.** Irritant cathartics are derived from plants and are activated in the GI tract to release irritant derivatives which activate myenteric neurons and smooth muscle to increase gut motility. They are used primarily in nonruminant large animals.
2. Castor oil is cleaved by pancreatic lipases in the small intestine to yield irritant ricinoleates. These stimulate peristalsis throughout the intestine and reduce fluid absorption. It is used mainly in calves and foals.
3. Anthraquinone (emodin) laxatives include aloe, senna, and cascara sagrada. These contain glycosides which are hydrolyzed in the large intestine to yield irritant anthraquinones which stimulate myenteric plexuses and increase colonic motility. Their onset of action is slow since they act in the large intestine. They are used mainly in horses.

XI. ANTIDIARRHEAL AGENTS

A. General considerations (Figure 11-5)

1. **Diarrhea** is defined as an increase in the frequency, volume, or fluidity of stools. General causes for diarrhea include (1) increased secretion of fluid and electrolytes—example is enterotoxigenic *E. coli* infection; (2) increased intestinal permeability—example is canine protein-losing enteropathy; (3) osmotic diarrhea—example is exocrine pancreatic insufficiency; and (4) alterations in intestinal motility—uncommon. **Acute diarrhea** may respond to symptomatic therapy with antidiarrheal drugs but **chronic diarrhea** requires a definitive diagnosis (often necessitating intestinal mucosal biopsy) and specific therapy.
2. **Oral rehydration** therapy with glucose–electrolyte solutions represents a significant advance in treating secretory diarrheal disease in the absence of vomiting.

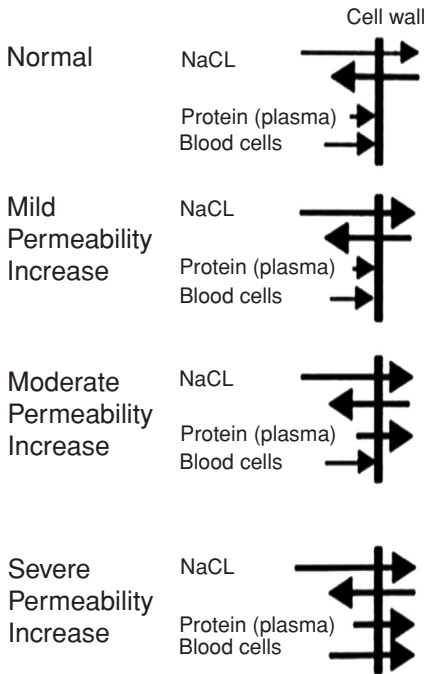


FIGURE 11-5. Altered intestinal permeability can lead to diarrhea. In the healthy intestinal mucosa, selective mucosal permeability leads to minor fluxes of electrolytes and water across the intact epithelial barrier. However, with mucosal inflammation (e.g., infiltrative mucosal diseases or intestinal ulceration with GI bleeding), larger molecular weight substances (albumin, globulins, red blood cells) are progressively lost into the GI lumen as intestinal permeability increases.

Sodium—glucose or fructose and sodium—amino acid-linked absorption by the enterocyte remains intact even in the presence of moderate loss of villus structure. This provides the driving force for water and electrolyte absorption from the lumen to replace fecal losses. In addition to glucose and/or amino acids, solutions contain sodium chloride, potassium chloride, sodium bicarbonate, and potassium phosphate.

B. Motility-modifying drugs (opiates) (See Chapter 4, V for information on opiates)

1. **Mechanism of action.** Opiates increase GI rhythmic segmentation and decrease propulsive motility via reduced acetylcholine release. Thus they slow the transit of luminal contents and increase water absorption. In addition, they directly stimulate net absorption of fluid and electrolytes via μ -opiate receptors in the CNS and the intestinal mucosa.
2. **Therapeutic uses.** Opiates are effective in the short-term (5–7 days) symptomatic treatment of acute diarrhea. Opiates are contraindicated in animals with infectious diarrhea because slowing GI transit may increase absorption of bacterial toxins and enhance bacterial growth in the intestinal lumen.
3. **Administration**
 - a. **Paregoric** (camphorated tincture of opium) is administered orally two or three times a day to dogs and cats and once a day to calves and foals.
NOTE: The use of antidiarrheal opiates in cats is controversial because of potential excitatory reactions.
 - b. **Diphenoxylate** is a synthetic congener of meperidine. It is combined with atropine as a commercial preparation LomotilTM and is given orally two to three times a day to dogs. Atropine is added at low concentrations to reduce the abuse potential in humans. Pharmacokinetic data for animals are lacking. In humans, diphenoxylate is well absorbed orally with peak plasma levels in 1–2 hours. It is rapidly deesterified to its active metabolite, difenoxin, which is eliminated with a $t_{1/2}$ of 12 hours.
 - c. **Loperamide** is a synthetic piperidine opioid with action limited to the gut. Pharmacokinetic data for animals are not available. In humans, loperamide is absorbed orally with peak plasma levels in 3–5 hours. It undergoes extensive

hepatic metabolism with a $t_{1/2}$ of 11 hours. Loperamide (Imodium.TM) is given orally once or twice a day to dogs at a dosage of 0.08 mg/kg.

4. **Adverse effects.** Constipation, bloat, and sedation are the most common side effects. Paralytic ileus, toxic megacolon, and pancreatitis are rare but potential adverse effects. Opiates should be used cautiously in cats because of the possibility of excitatory reactions in this species.

C. Anticholinergic agents

1. **Mechanism of action.** Anticholinergic agents inhibit GI motility, both propulsive and nonpropulsive. The rationale for their use as antidiarrheals is questionable since hypomotility of the gut is common, especially in diarrheal diseases. Inhibition of cholinergically mediated basal secretions of GI tract may be beneficial but controlled studies are lacking.
2. **Therapeutic uses.** Anticholinergic agents are employed as antidiarrheals and GI antispasmodics.
3. **Administration**
 - a. **Isopropamide**—dogs and cats, orally every 12 hours.
 - b. **Aminopentamide**—dogs and cats, orally, IM, or SC every 8–12 hours.
 - c. **Propantheline**—dogs and cats, orally every 8 hours.
 - d. **Methscopolamine**—dogs, orally every 8–12 hours.
4. **Adverse effects.** Xerostomia, tachycardia, loss of accommodation, urinary retention, and paralytic ileus may be observed as side effects of anticholinergic drugs.

D. Protectants and adsorbents

1. **Mechanism of action.** Protectants and adsorbents adsorb toxins and provide a protective coating on the inflamed mucosa. They are widely used but their efficacy is questionable. They may decrease fluidity of feces without decreasing fecal water loss.
2. **Therapeutic uses.** Protectants and adsorbents are used for the symptomatic therapy of acute diarrhea.
3. **Administration**
 - a. **Kaolin/Pectin—Kaolin** (hydrated aluminum silicate) 20% is combined with pectin (polygalacturonic acid carbohydrate polymer) 1% is Kaopectate. It is administered to dogs, cats, birds, horses, cattle, sheep, and swine orally every 4–6 hours.
 - b. **Bismuth subsalicylate** has an antiprostaglandin action in addition to its protective/adsorbent properties. It is also used as a component of “triple therapy” for treatment of helicobacteriosis. It is given orally to dogs, horses, cattle, swine, and cats (reduced dosage) every 6–8 hours. Note that cats are sensitive to salicylates.
4. **Adverse effects.** Kaolin/pectin—none; bismuth subsalicylate may produce dark stools which should not be confused with melena. Salicylates should be used cautiously in cats.

XII. DRUGS FOR THERAPY OF INFLAMMATORY BOWEL DISEASE

- A. **General considerations.** The IBD represent a diverse group of chronic GI diseases of unknown cause. Both clinical and basic science studies indicate that IBD results from complex interactions between the resident gut flora and the intestinal immune system in a susceptible host. Idiopathic IBD is the most common histologic diagnosis made in dogs and cats having chronic GI signs of vomiting, diarrhea, anorexia, and weight loss. A diagnosis of IBD is one of exclusion and it is only made following rigorous diagnostic evaluation to rule out IBD mimics. Treatment of IBD consists of feeding an elimination (hypoallergenic) diet and the administration of immunomodulatory drugs to reduce intestinal inflammation.

B. Sulfasalazine

1. **Chemistry.** Sulfasalazine consists of sulfapyridine plus 5-aminosalicylic acid (5-ASA) linked by a diazo bond.
2. **Mechanism of action.** Sulfasalazine is cleaved by bacteria in the large bowel to release sulfapyridine and salicylate. The anti-inflammatory effects of salicylate (5-ASA) on the bowel mucosa are considered to be primarily responsible for the therapeutic action of sulfasalazine. Salicylates act by inhibiting prostaglandin synthesis and the effects of proinflammatory leukotrienes in the colonic mucosa.
3. **Therapeutic uses and administration.** Sulfasalazine is administered orally two to three times a day for chronic IBD involving the colon (e.g., IBD colitis) in dogs and cats. It is of no therapeutic value to animals having small intestinal IBD.
4. **Pharmacokinetics.** Sulfasalazine is classed as an enteric sulfonamide since oral absorption is generally <30% for sulfapyridine. Salicylate absorption is <10%.
5. **Adverse effects.** Side effects are rare but sulfapyridine toxicity, especially keratoconjunctivitis sicca (KCS), may develop with long-term use. Prophylactic Schirmer tear testing should be performed prior to using this medication. Cats should be monitored for signs of salicylate toxicity if therapy is prolonged.

C. Olsalazine

1. **Chemistry.** Olsalazine consists of two molecules of 5-aminosalicylate linked by a diazo bond. Developed for use in humans with IBD where up to 25% may show adverse reactions to sulfasalazine.
2. **Mechanism of action.** After cleavage of the diazo bond by colonic bacteria, salicylates are released to reduce inflammation in the bowel mucosa by inhibition of prostaglandin synthesis.
3. **Therapeutic uses and administration.** Olsalazine is administered orally two to three times a day for chronic IBD in dogs and cats. Controlled studies in the dog attesting to the efficacy of this drug have not been performed.
4. **Pharmacokinetics.** Oral absorption of olsalazine is minimal with over 98% of the dose reaching the colon.
5. **Adverse effects.** Olsalazine is less toxic than sulfasalazine since it lacks the sulfonamide moiety. Cats should be monitored for signs of salicylate toxicity if therapy is prolonged.

D. Tylosin (see Chapter 15, XI for more information)

1. **Chemistry.** Tylosin is a macrolide antibiotic structurally related to erythromycin (see Chapter 15). Macrolides are organic bases which form salts with acids such as phosphate or tartrate.
2. **Mechanism of action.** Tylosin inhibits protein synthesis in susceptible bacteria by binding to the 50S ribosome and blocking long-chain peptide synthesis. Its bacteriostatic action suppresses bacterial overgrowth in chronic intestinal disease. It is thought to possess immunomodulatory actions in IBD patients—possibly related to its antibacterial properties rather than to suppression of the host immune response.
3. **Therapeutic uses and administration.** Tylosin is administered orally with food two or three times a day for chronic colitis in dogs and cats.
4. **Pharmacokinetics.** Tylosin is absorbed from the intestine and widely distributed except to the CNS. It is eliminated unchanged in bile and urine.
5. **Adverse effects.** Mild GI disturbances such as nausea or diarrhea may be observed with tylosin.

E. Metronidazole

1. **Mechanism of action.** Metronidazole is an antiprotozoan nitroimidazole (see Chapter 16) and antibacterial, especially against anaerobes (Chapter 15). It may also suppress cell-mediated immune responses which are important in IBD.

2. **Therapeutic uses and administration.** Metronidazole (Flagyl®) is administered orally two to three times a day for the treatment of colitis in dogs.
3. **Pharmacokinetics.** Metronidazole is well absorbed orally, widely distributed to a volume equivalent to total body water. Hepatic metabolites and unchanged drug are excreted in urine and feces. The plasma $t_{1/2}$ in dogs is 4–5 hours
4. **Adverse effects.** Side effects are infrequent in dogs. High or prolonged doses may produce neurotoxicity including tremors and ataxia. Metronidazole should not be used in pregnant animals.

F. FortiFlora®

1. FortiFlora is a specific probiotic (*Enterococcus faecium* SF68) which is marketed for dogs and cats with GI disorders. This preparation uses a unique microencapsulated formula which conserves and protects the biologically active *E. faecium* SF68 so it can withstand handling, processing, and storage.
2. **Probiotics** are live bacterial products that affect beneficial health responses to the host. They have diverse ways in which they evoke these changes including exclusion of bacterial pathogens and enhancement of local immunity.
3. Preliminary clinical data suggest that FortiFlora™ is of potential therapeutic benefit in both acute and chronic GI diseases, including IBD. While clinical trials have not been performed in dogs or cats with IBD, evidence-based data in human IBD indicate that probiotics are useful in reducing severity of clinical disease.

XIII. RUMEN PHARMACOLOGY

A. General considerations

1. Development of rumen function starts at 3–6 weeks and is complete at 9–13 weeks.
2. Normal intraruminal pH range is 5.5–7.
3. Extrinsic contractions of the ruminoreticulum are controlled by vagal efferents from the dorsal vagal nucleus in the CNS.
4. Intrinsic contractions are controlled by intramural plexuses.
5. Rumen microflora function depends upon a proper nutrient intake and normal ruminoreticular motor activity.

B. Agents for closure of esophageal groove

1. Closure of the esophageal groove is required for oral medication of calves and lambs in order to bypass the nonfunctioning ruminoreticulum.
2. When stimulated, buccal and pharyngeal receptors activate a vagal reflex to close the groove starting in 2–5 seconds and lasting for 60 seconds.
3. **Administration**
 - a. **Milk**—calves and lambs, orally
 - b. **Sodium bicarbonate**—10% calves, orally
 - c. **Copper sulfate**—5% calves, 2% lambs, orally
 - d. **NOTE:** Water is not an effective stimulus for groove closure.

C. Ruminotorics

1. **Bitters** are plant-derived compounds containing alkaloids such as nux vomica, ginger, or capsicum which stimulate salivation. They were components of large animal tonic mixtures for the treatment of inappetence and depressed rumen function. Their efficacy is doubtful and they are seldom used now.
2. **Cholinergics** such as neostigmine or bethanechol (Chapter 2) transiently increase the frequency but not the strength of contractions in rumen atony. Since they do not provide the synchronized contractions and relaxations of the

forestomachs, their value for the movement of ingesta is limited. They are administered SC.

3. **Experimentally, metoclopropamide has been reported to increase ruminoreticular motility and abomasal contractions.** Opiate antagonists such as naloxone stimulate extrinsic contractions in endotoxin-induced ruminal stasis when administered parenterally.
4. **Ruminal fluid transfer.** Oral inoculation of viable rumen bacteria and protozoa is the most effective means of restoring rumen function following correction of the primary cause of stasis.

D. Rumen antacids

1. The principal use of antacids in ruminants is in treating mild cases of lactic acidosis resulting from carbohydrate engorgement.
2. **Administration.** Orally every 8–12 hours
 - a. Magnesium oxide (MgO)
 - b. Magnesium carbonate
 - c. Aluminum hydroxide
3. **Adverse effects.** Systemic alkalosis may occur with overdose, especially with MgO.

E. Rumen acidifiers

1. The principal use of ruminal acidifiers is in treating simple indigestion in which intraruminal pH rises due to the constant inflow of bicarbonate-rich saliva. They are also used in the treatment of acute urea poisoning to decrease ammonia absorption via formation of ammonium ion and to inhibit urease activity of the rumen microflora.
2. **Administration.** Vinegar or dilute acetic acid (4–5%) is administered at a dose of 4–8 liters in cattle via stomach tube every 6–8 hours with several liters of cold water.

F. Bloat therapy

1. Ruminal bloat or tympany is the accumulation of excess gas in the rumen as a result of impaired elimination, *not* excess production. Ruminal gasses may be in the free form or, more commonly, entrapped in froth. Passage of a ruminal tube will alleviate free-gas bloat but viscosity-altering agents are required for the treatment of frothy bloat.
2. **Mechanism of action.** Anti-bloat agents alter the surface tension of froth and break up the bubbles which contain entrapped gases.
3. **Administration.** Anti-bloat agents are administered via drench or stomach tube.
 - a. Poloxalene (25–50 g for cattle).
 - b. Polymerized methyl silicone (3% emulsion; 30–60 mL in cattle; 7–15 mL in sheep).
 - c. Vegetable oils (soybean, peanut, or sunflower oil); 60 mL in cattle; 10–15 mL in sheep.

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