

# Systemic Pharmacotherapeutics of the Respiratory System

Drugs used to treat respiratory tract diseases fall into several categories: antitussives, bronchodilators, anti-inflammatories, expectorants, decongestants, and respiratory stimulants. In addition, antimicrobials and antifungals are important in the therapy of many respiratory diseases.

## 1. Antitussive Drugs

A **cough** is a sudden, explosive exhalation of air that functions to clear material from the airways. Coughing is one way in which the lungs and airways are protected from inhaled particles. Coughing sometimes brings up sputum (also called phlegm), a mixture of mucus, debris, and cells expelled from the lungs. The cough reflex has both sensory (afferent) and motor (efferent) pathways.

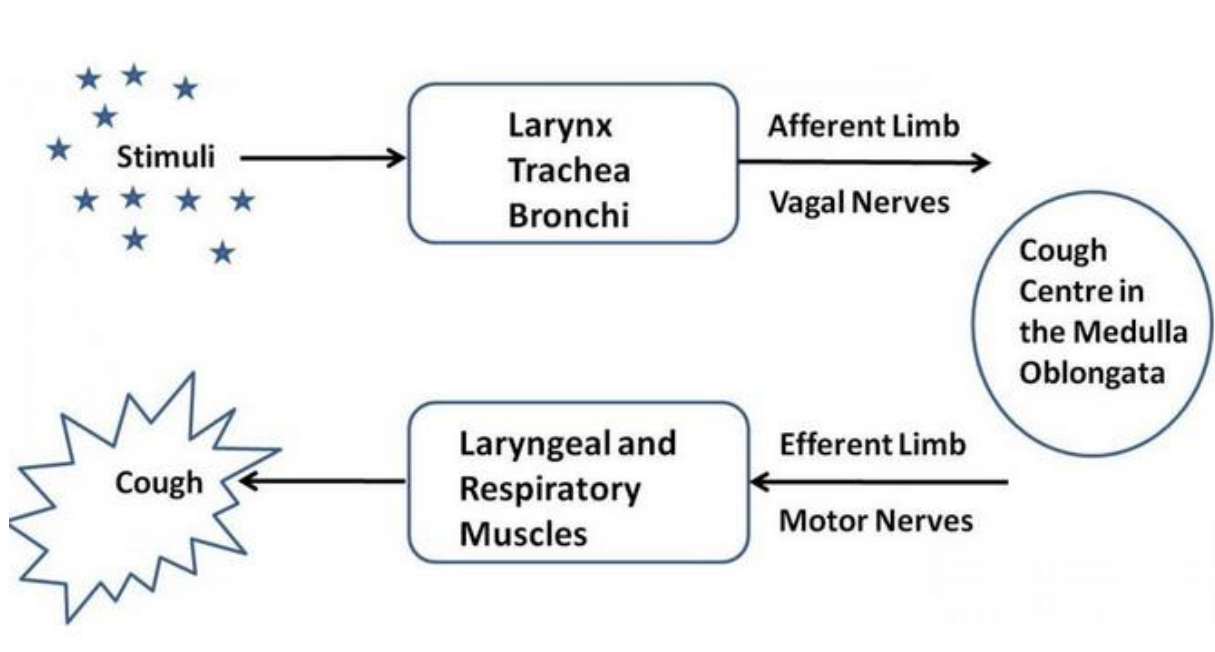


Fig. The sensory and motor pathways of the cough reflex.

The internal laryngeal nerve carries the sensory information away from the area above the glottis in the trachea to the cough center located in the medulla oblongata via the vagus nerve. Stimulation of this area by dust or foreign particles produces a cough to remove the foreign material from the respiratory tract before it reaches the lungs. Mucus production in the bronchi is an airway defense mechanism, and it increases with inflammation and infection. In dogs and cats, coughing occurs because of a primary disease process, such as *Bordetella bronchiseptica* infection ("kennel cough") or chronic bronchitis in dogs, or feline asthma or heartworm-associated respiratory disease in cats. In most cases, addressing the primary disease will resolve the cough. Antitussive therapy is symptomatic and is primarily for the comfort of the animal and the owner. Most antitussive drugs are opiates or opioids that directly suppress the cough center in the medulla oblongata (see Table: Antitussive Drugs). The antitussive effect does not appear to be related to the binding of traditional opiate receptors (mu and kappa). For example, dextromethorphan is an opioid derivative with good antitussive activity, but it does not have activity at opiate receptors and is not analgesic or addictive.

**Morphine** is an effective antitussive at doses lower than those that produce analgesia and sedation. It is not commonly used for antitussive activity because of adverse effects and the potential for abuse and addiction. Morphine has poor oral bioavailability due to a significant first-pass effect by the liver.

**Codeine** is methylmorphine; methylation of morphine significantly improves the oral bioavailability by reducing the first-pass effect. Codeine phosphate and codeine sulfate are found in many preparations, including tablets, liquids, and syrups. Codeine has analgesic effects that are about one-tenth that of morphine, but its antitussive potency is about equal to that of morphine. The adverse effects of codeine are significantly less than those seen with morphine at antitussive doses. Toxicity (especially in cats) is exhibited as excitement, muscular spasms, convulsions, respiratory depression, sedation, and constipation. Codeine should not be used after GI tract surgery because of its effects on intestinal motility. The potential for addiction and abuse of codeine is considerably lower than that for morphine.

**Hydrocodone** is chemically and pharmacologically similar to codeine but more potent. It is combined with an anticholinergic drug (homatropine) to discourage abuse by people. It can be prescribed for small animals but should be used with caution in cats.

**Dextromethorphan** is technically not considered an opiate, because it does not bind to traditional opiate receptors and is not addictive or analgesic. It is the d-isomer of levorphanol. The l-isomer of levorphanol has addictive and analgesic properties. Although it is recommended anecdotally to treat cough, a pharmacokinetic study in dogs demonstrated a short elimination half-life, rapid clearance, and poor oral bioavailability, making its use as an orally administered cough suppressant in dogs questionable.

**Butorphanol**, an opioid agonist-antagonist, is used as an analgesic and antitussive in dogs. As an antitussive in dogs, butorphanol is 4 times more potent than morphine and 100 times more potent than codeine. At antitussive dosages, it may produce considerable sedation in dogs. Because butorphanol has poor bioavailability, the oral dose in dogs is 10 times the SC dose. In cats, butorphanol is primarily used as an injectable analgesic. In some cats, it may cause pain on injection, as well as mydriasis, disorientation, swallowing/licking, and sedation.

Drug	Dosage
<a href="#">Codeine</a>	Dogs: 1–2 mg/kg, PO, bid-qid
Hydrocodone	Dogs: 0.25 mg/kg, PO, bid-qid
<a href="#">Butorphanol</a>	Dogs: 0.055–0.11 mg/kg, SC, bid-qid, or 0.55–1.1 mg/kg, PO, bid-qid Cats: 0.1–0.4 mg/kg, SC, bid-qid

## 2.Species Approach to Inflammatory Airway Disease

Dogs, cats, horses, and people develop spontaneous bronchoconstriction associated with airway inflammation and characterized by chronic cough and wheeze. Attacks of airway obstruction are induced by exposure of susceptible animals to antigens (typically hay dust, molds, and pollens). Effective therapy of allergic airway disease is species dependent because of the inflammatory mediators involved in bronchoconstriction. The pathogenesis of feline asthma differs from allergic airway disease in other species in that cats are exceptionally responsive to serotonin (5-hydroxytryptamine). Serotonin, which is released from degranulating mast cells, appears to be the major mediator of allergen-induced bronchoconstriction in cats. Cats also appear to suffer from chronic bronchitis, similar in clinical presentation to feline asthma; the main feature that differentiates these two conditions is the lack of bronchoconstriction in chronic bronchitis. In dogs, chronic bronchitis is an inflammatory, chronic pulmonary disease that results in cough and can lead to exercise intolerance and respiratory distress but is typically not characterized by severe bronchoconstriction. In horses, there are two clinical syndromes of airway inflammation. Recurrent airway obstruction, or “heaves,” is an inflammatory, obstructive airway disease clinically evident in middle-aged horses. Inflammatory airway disease is a low-grade inflammation of the small airways that is a common cause of poor performance in young to middle-aged, athletic horses. Inflammatory airway disease is typically not treated in ruminants or swine.

The goals of therapy for inflammatory airway disease are to prevent recurrent exacerbations of airway obstruction and reduce emergency visits and expenses, to provide optimal chronic anti-inflammatory therapy with minimal or no adverse effects, to maintain (near) “normal” pulmonary function, and to meet the owner's expectations of quality of life for their animal.

## Systemic Therapy of Inflammatory Airway Disease

### **β-Adrenergic Receptor Agonists**

The β-adrenergic receptor agonists have beneficial effects in treatment of bronchoconstrictive respiratory tract diseases (see Table: β-Adrenergic Receptor Agonist Drugs). Bronchial smooth muscle is innervated by β<sub>2</sub>-adrenergic receptors. Stimulation of these receptors leads to increased activity of the enzyme adenylate cyclase, increased cAMP, and relaxation of bronchial smooth muscle. Stimulation of β receptors on mast cells decreases the release of inflammatory mediators from mast cells, but other inflammatory cells are not suppressed. There is some evidence that β-adrenergic receptor agonists increase mucociliary clearance in the respiratory tract. The β-adrenergic receptor agonists should be used with caution in animals with preexisting cardiac disease, diabetes mellitus, hyperthyroidism, hypertension, or seizure disorders, or that are being treated with digoxin, tricyclic antidepressants, or monoamine oxidase inhibitors.

Table.  $\beta$ -Adrenergic Receptor Agonist Drugs

Drug	Dosage
<a href="#">Epinephrine</a>	Dogs: 0.05–0.5 mg, intratracheally or IV
	Cats: 0.1 mg, IV or IM
	Large animals: 0.1 mg/kg, IV, SC, or IM
<a href="#">Isoproterenol</a>	Dogs: 0.1–0.2 mg, IM or SC, qid
	Cats: 4–6 mcg, IM, every 30 min as needed
	Horses: 0.4 mcg/kg, IV (diluted)
<a href="#">Terbutaline</a>	Dogs, cats: 0.1 mg/kg, SC, every 4 hr, or 0.03 mg/kg, PO, tid
	Horses: 0.0033 mg/kg, IV, or 0.2–0.6 mg/kg, PO, bid
<a href="#">Albuterol</a>	Dogs: 0.05 mg/kg, PO, tid
	Horses: 8 mcg/kg, PO, bid
Clenbuterol	Horses: 0.8–3.2 mcg/kg, PO, bid

**Epinephrine** (adrenaline) stimulates  $\alpha$  and  $\beta$  receptors, resulting in pronounced vasopressive and cardiac effects in addition to bronchodilation. Epinephrine is reserved for emergency treatment of life-threatening bronchoconstriction (eg, anaphylaxis). The nonspecific stimulation of other receptors and its short duration of action make it unsuitable for longterm use. Epinephrine is available as a 1 mg/mL solution. Its onset of action is immediate, and the duration of effect is 1–3 hr.

**Isoproterenol** is a potent  $\beta$ -receptor agonist. It is selective for  $\beta$  receptors, but cardiac ( $\beta_1$ ) effects make it unsuitable for longterm use. It is administered by inhalation or injection and has a short duration of action (<1 hr). For emergency relief of bronchoconstriction in horses, it is given by slow IV solution at a dilution of 0.2 mg/50 mL of saline. Administration is discontinued when the heart rate doubles.

**Terbutaline** is a  $\beta_2$ -receptor agonist similar to isoproterenol but longer acting (6–8 hr). It may be available in some countries as an injectable solution, powder inhaler, or oral syrup and tablets. For cats with feline asthma that experience frequent, severe bronchoconstrictive episodes despite chronic glucocorticoid therapy, injectable terbutaline can be dispensed to owners with instructions to administer 0.01 mg/kg, SC, to treat episodes of bronchoconstriction at home. An increase in the cat's heart rate to 240 bpm and a 50% decrease in respiratory rate indicates a positive effect. Terbutaline also can be given as chronic oral therapy at 0.625 mg/cat, bid (¼ of a 2.5-mg tablet). It should not be used in cats with hypertrophic cardiomyopathy or glaucoma, in which  $\beta_2$ -receptor stimulation would be detrimental.

**Albuterol** (salbutamol) is similar to terbutaline and may be used systemically in dogs and horses. Oral syrup, oral tablets, and oral extended-release tablets are available, but albuterol is more commonly used as inhalation therapy.

**Clenbuterol** is used in the treatment of recurrent airway obstruction in horses; it is not used in dogs and cats. It is available as an oral syrup and may be available as an injectable solution for IV injection in some countries. Results of efficacy studies for bronchoconstriction have been conflicting, but clenbuterol appears to significantly increase mucociliary transport in horses with the disorder. The dosage is increased gradually until a satisfactory clinical response is seen. If there is no response at the highest recommended dose, the horse is considered to have irreversible bronchospasm. It should not be administered chronically to horses with recurrent airway obstruction without concurrent anti-inflammatory therapy. The most common adverse effects of clenbuterol are tachycardia and muscle tremors. Clenbuterol inhibits uterine contractions, so it should be used during late pregnancy only if this effect is desired for obstetric manipulations. Clenbuterol is also a repartitioning agent; it directs nutrients away from adipose tissue and toward muscle. The result is increased carcass weight, increased ratio of muscle to fat, and increased feed efficiency. Because there is a significant human health risk from clenbuterol residues, it is banned in food animals in most countries and should not be used in horses that will be sent to slaughter.

## Methylxanthines

The methylxanthines, particularly theophylline, are bronchodilators (see Table: Methylxanthine Bronchodilators). Once the mainstay of human asthma therapy, theophylline has a high incidence of adverse effects, and its use has diminished with the development of metered-dose or disk inhalers for local drug delivery. The methylxanthines have a variety of pharmacologic effects on various organ systems, including bronchial smooth muscle relaxation, CNS stimulation, mild diuresis, and mild cardiac stimulation.

Table. Methylxanthine Bronchodilators

## Methylxanthine Bronchodilators

Drug	Dosage
<a href="#">Theophylline</a> (parenteral)	Dogs: 10 mg/kg, IV (slow) or IM
	Horses: 15 mg/kg, IV (slow)
<a href="#">Theophylline</a> (oral)	Dogs: 5–7 mg/kg, PO, tid
	Cats: 3 mg/kg, PO, bid
	Horses: 10–15 mg/kg, PO, bid
<a href="#">Theophylline</a> (extended-release tablets)	Dogs: 20 mg/kg/day, PO
	Cats: 25 mg/kg/day, PO
	Horses: 15 mg/kg/day, PO
<a href="#">Aminophylline</a> (parenteral)	Dogs: 10 mg/kg, IV (slow)
	Cats: 5 mg/kg, IV (slow)
	Horses: 5 mg/kg, IV (slow)
<a href="#">Aminophylline</a> (oral)	Dogs: 10 mg/kg, PO, tid
	Cats: 5 mg/kg, PO, bid
	Horses: 15 mg/kg, PO, bid

The respiratory effects of methylxanthines are the result of several cellular mechanisms. Antagonism of adenosine is currently thought to be the most important action. Adenosine induces bronchoconstriction in asthmatic animals and antagonizes adenylate cyclase. Adenylate cyclase is responsible for the synthesis of cAMP, which controls bronchial smooth muscle relaxation and inhibits the release of inflammatory mediators from mast cells. Methylxanthines also inhibit phosphodiesterase, which further increases intracellular cAMP. They also inhibit calcium mobilization in smooth muscle, inhibit prostaglandin production, augment the release of catecholamines from storage granules, and increase the availability of calcium to contractile proteins of the heart and diaphragm. In addition to promoting bronchial smooth muscle relaxation, methylxanthines decrease the release of inflammatory mediators from mast cells and increase mucociliary transport.

**Theophylline** is available in several formulations, including injectable, aqueous solutions, elixirs, tablets, and capsules. Theophylline base is poorly soluble in water and often results in GI irritation when administered PO. Aminophylline is a theophylline salt that is 78%–86% theophylline. It is more water soluble and results in less GI irritation. Other theophylline salts, such as oxtriphylline (a choline salt), are available, and their theophylline content must be considered when developing a drug dosage regimen.

Several sustained-release formulations of theophylline are suitable for use in dogs and cats and may be administered less frequently than the regular formulations. After oral administration, theophylline is rapidly and completely absorbed. Therapeutic plasma concentrations, extrapolated from people, are 5–20 mcg/mL. Animals are sensitive to high concentrations of theophylline, especially after rapid IV administration, and toxicity may be seen with

concentrations <20 mcg/mL. Theophylline tablets may become trapped in bezoars (such as hairballs in cats), and continued absorption can result in toxicity. Cardiac arrhythmias, CNS excitement, tremors, convulsions, and GI irritation may be seen. Theophylline undergoes enterohepatic recirculation, so activated charcoal is recommended if clinical signs are present, no matter how long after the drug was administered. Theophylline metabolism is inhibited by erythromycin, cimetidine, propranolol, enrofloxacin, and marbofloxacin; concomitant therapy can result in theophylline toxicity. Theophylline metabolism is induced by rifampin and phenobarbital, which may necessitate increasing the dose of theophylline.

Theophylline is used to treat both cardiac and respiratory diseases in dogs and cats. Theophylline is also used in management of intrathoracic collapsing trachea and various forms of canine bronchitis, but it is less effective than glucocorticoids such as prednisone. Theophylline or aminophylline was used in horses in the management of recurrent airway obstruction, but efficacy was often poor and use of these drugs has been replaced by  $\beta$ -agonist bronchodilators delivered by metered-dose inhalers.

## Anticholinergic Drugs

The anticholinergic (parasympatholytic) drugs are effective bronchodilators that reduce the sensitivity of irritant receptors and inhibit vagally mediated cholinergic smooth muscle tone in the respiratory tract. Cholinergic stimulation causes bronchoconstriction; asthmatic individuals appear to have excessive stimulation of cholinergic receptors.

**Atropine** is primarily used as a preanesthetic to prevent bradycardia and reduce airway secretions, and as emergency therapy of dyspneic animals with organophosphate intoxication. Atropine is also used for bronchodilation in horses; a low IV dose (0.014 mg/kg) is more effective and less toxic than IV theophylline. A test dose of 0.022 mg/kg may also be used to determine prognosis in horses with recurrent airway obstruction; if pulmonary function does not improve with a test dose of atropine, successful management with bronchodilators is unlikely. Atropine should be used with caution, because even low doses may cause tachycardia, ileus, neurologic derangement, and blurred vision in horses.

**Glycopyrrolate** is twice as potent as atropine in people and does not cross the blood-brain barrier. Its onset of action is slower than atropine, but its duration of effect is longer. Information about use in horses is sparse, but doses of 2–3 mg can be given IM, bid-tid.

**N-butylscopolammonium bromide** is an anticholinergic drug approved to relieve spasmodic colic in horses. Unlike atropine, N-butylscopolammonium bromide does not cross the blood-brain barrier. Adverse effects are minimal and include transient tachycardia, decreased borborygmi, and transient pupillary dilatation. In horses with recurrent airway obstruction challenged with moldy hay, N-butylscopolammonium bromide was a potent bronchodilator, with maximum relief occurring 10 min after IV administration. The bronchodilatory effect is short lived, dissipating within 1 hr of drug administration.

## Glucocorticoids

The glucocorticoids inhibit the release of inflammatory mediators from macrophages and eosinophils but do not inhibit the release of granules from mast cells. Glucocorticoids decrease synthesis of prostaglandins, leukotrienes, and platelet-activating factor, which play important roles in the pathophysiology of respiratory tract inflammation. Studies suggest glucocorticoids



enhance the action of adrenergic agonists on  $\alpha_2$ -receptors in the bronchial smooth muscle. Because of immunosuppressive effects, glucocorticoids are generally avoided in infectious respiratory diseases.

For severe attacks of canine bronchitis, feline asthma, or recurrent airway obstruction, parenteral injection of glucocorticoids usually provides rapid relief. For chronic therapy in dogs, oral prednisone is usually the drug of choice. Prednisone is a prodrug; it is metabolized by the liver to the active drug prednisolone. Pharmacokinetic studies have shown poor oral bioavailability of prednisone in cats and horses. Therefore, it is preferable to administer prednisolone to these species. In dogs, a typical anti-inflammatory dosage is 0.5–1 mg/kg, with chronic therapy on an every-other-day basis. A similar dose of prednisolone can be used in cats; if prednisone is used, higher doses may be necessary. Cats are somewhat resistant to the effects of glucocorticoids, and dosages of prednisone of 1 mg/kg/day may be necessary for chronic therapy of feline asthma. Alternatively, 20 mg of methylprednisolone acetate can be administered IM to asthmatic cats every 3 wk. For emergency treatment of dyspneic cats, a shock dose of an IV glucocorticoid (prednisone sodium succinate, 5–10 mg/kg; or dexamethasone sodium phosphate, 1–2 mg/kg) should be used. It is common for clinical signs to resolve in cats with feline asthma or chronic bronchitis that are treated with oral glucocorticoids despite persistent lower airway inflammation, so therapy should be tapered very carefully. Although prednisolone can be administered to horses, the small tablet sizes available make it inconvenient, so equine formulations of oral dexamethasone (10 mg/450 kg) are recommended. The injectable formulation of dexamethasone can be given IV to horses with acute bronchoconstriction and dyspnea. Flumethasone or isoflupredone may also be used in horses. Isoflupredone is as effective as dexamethasone in the treatment of recurrent airway obstruction in horses, but as in cattle, it is associated with hypokalemia.

## Cyproheptadine

Because of the role of serotonin in allergen-induced bronchoconstriction in cats, the serotonin antagonist/antihistamine cyproheptadine (2 mg, PO, once to twice daily) may be used as an adjunct to glucocorticoids and bronchodilators to block bronchoconstriction in chronically asthmatic cats. In experimental models of feline asthma, cyproheptadine decreased airway hyperreactivity but did not significantly decrease eosinophilic airway inflammation. However, pharmacokinetic studies of cyproheptadine suggest that some cats may require doses as high as 8 mg to reach therapeutic concentrations. Because of its long elimination half-life (12 hr), cyproheptadine requires several days to reach steady-state concentrations, and 4–7 days may be needed to see clinical effects. Serotonin antagonism in the appetite center stimulates appetite, so weight gain may be a problem. Lethargy, depression, and increased appetite may occur within 24 hr of initiating therapy.

## Antimicrobial Therapy

Antimicrobial therapy may or may not be necessary in treatment of airway inflammatory diseases. Antimicrobial therapy should be started for cats with tracheobronchial cultures suggestive of a true bacterial infection or those positive for *Mycoplasma*. *Mycoplasma* spp can be isolated from healthy dogs but are not found in healthy cats. Doxycycline, azithromycin, and fluoroquinolones treat *Mycoplasma* infections effectively. Secondary bacterial infection from *Streptococcus zooepidemicus* may exacerbate inflammatory airway disease in horses and can easily be treated with penicillin, ceftiofur, or a trimethoprim/sulfonamide.



# Inhalation Therapy of Airway Disease

The current approach to management of inflammatory airway disease is through inhalation therapy with nebulizers or metered-dose inhalers (MDIs). With inhalation therapy, high drug concentrations are delivered directly to the lungs via nebulizers or MDIs, and systemic adverse effects are avoided or minimized. The onset of action for inhaled bronchodilators and anti-inflammatory drugs is substantially shorter than that of oral or parenteral formulations. Nebulizers have long been used in animals, but the overall efficiency of drug delivery is low, and the equipment is cumbersome and inconvenient for owners. Administration of medications via MDIs is commonplace in treatment of human asthma and seems to benefit management of animals as well. Human MDIs are designed to provide optimal lung delivery after actuation during a slow, deep inhalation. However, this is impossible to control in animals. The addition of spacers enables MDIs to be used in animals. Spacers decrease the amount of drug deposited in the oropharynx (up to 80% of the actuated dose with the MDI alone), thereby reducing systemic drug absorption. Drugs available in MDI formulations include  $\beta_2$ -agonists, glucocorticoids, ipratropium bromide, cromolyn sodium, and nedocromil. Each product delivers a set amount of drug per actuation (puff). In the USA, MDIs are labeled according to the amount of drug delivered at the mouthpiece, whereas in Canada and the EU they are labeled according to the amount of drug delivered from the valve. MDIs are color-coded to aid identification. Even in human medicine, the relative potencies, risks of adverse effects, and optimal dose of the different inhaled asthma medications remain unclear. Unfortunately, some drugs that would be useful in veterinary patients are not available in MDIs; dry powder inhalers are not suitable for use in animals. Clinical use of MDI medications in asthmatic cats, dogs with chronic bronchitis, and horses with recurrent airway obstruction is promising but mostly anecdotal, and clinical trials are needed to determine the most efficacious therapies.

## $\beta_2$ -Agonists

Short-acting  $\beta_2$ -agonists such as **albuterol (salbutamol)** in MDIs are the medications of choice to treat acute exacerbations of bronchoconstriction, because they relax smooth muscle and promptly increase airflow. Although effective for symptomatic relief,  $\beta_2$ -agonists do not control inflammation. Airway obstruction may persist despite appropriate use of inhalant bronchodilators because of bronchial wall edema and airway mucus plugging. In general,  $\beta_2$ -agonists are extremely safe for use in animals when used as needed for bronchoconstriction. Toxicity typically requires a large overdose, such as when dogs chew on and puncture the inhaler, receiving a very large dose at one time (there are 200 doses in an albuterol/salbutamol inhaler). Massive overdose may induce severe tachycardia and hypokalemia, which, in turn, lead to extreme weakness, incoordination, and potentially cardiac standstill. Other less serious signs include dilated pupils, severe agitation and hyperactivity, hypertension, and vomiting.

Albuterol (salbutamol) is the medication of choice in all species for inhalation therapy of acute airway obstruction. It relaxes smooth muscle and increases airflow within minutes of administration; effects last 3–6 hr. Although effective for symptomatic relief, the  $\beta_2$ -agonists do not control inflammation, and monotherapy may exacerbate asthma and increase morbidity and mortality. Racemic albuterol (R, S albuterol) is the most commonly prescribed short-acting  $\beta_2$ -agonist and is composed of a 1:1 mixture of (R)-albuterol (the R-enantiomer) and (S)-albuterol (the S-enantiomer). The R-enantiomer has bronchodilatory and anti-inflammatory effects, and the S-enantiomer paradoxically is associated with increased airway hyperreactivity and pro-inflammatory effects. The paradoxical exacerbation of asthma with regular use of

inhaled racemic albuterol in people is thought to be linked to preferential accumulation of S-albuterol in the lung, which has a much slower metabolism than R-albuterol. Neutrophilic airway inflammation in healthy cats was induced when receiving treatment with albuterol containing the S-enantiomer. These data suggest that the form of albuterol commonly prescribed to asthmatic cats can actually cause inflammation in “healthy” cats without preexisting airway disease. The S-enantiomer also exacerbates eosinophilic airway inflammation in experimentally asthmatic cats. This increase in airway inflammation associated with use of albuterol can be attenuated by concurrent use of glucocorticoids. Proper control of the underlying inflammation should reduce albuterol use to an as-needed only basis. One actuation (100 mcg Canada; 90 mcg USA) of albuterol can be administered for relief of bronchoconstriction as needed until clinical signs resolve.

**Salmeterol** is a long-acting  $\beta_2$ -agonist; its onset of action is slow (15–30 min), but its duration of action is >12 hr. The long duration of action is due to diffusion into the plasma membrane of the pulmonary cells followed by slow release from the cells to interact with  $\beta_2$  receptors. It is not recommended for use in acute bronchoconstriction, but daily use with glucocorticoids provides better control of symptoms than simply increasing the glucocorticoid dose. It is not available in an MDI in all countries, and the dry powder inhaler is not suitable for animal use.

Other  $\beta_2$ -agonists that may be available in MDIs include isoproterenol, fenoterol, formoterol, and terbutaline. Isoproterenol was commonly used to treat asthma before the more widespread use of albuterol, which has more selective effects on the airways. In Europe, an epidemic of deaths due to cardiotoxicity from overuse of isoproterenol inhalers led to withdrawal of the products. North American products have clear warning labels regarding the potential toxicity.

## Glucocorticoids

Inhaled glucocorticoids are the most potent inhaled anti-inflammatory drugs available. In people, early intervention with inhaled glucocorticoids improves asthma control, normalizes lung function, and may prevent irreversible airway damage. The potential risk of adverse effects is well balanced by their efficacy in management of chronic inflammation. Oral candidiasis (thrush), dysphonia, and reflex cough and bronchospasm are the most common adverse effects in people; all of these effects are reduced by use of a spacer. The risk of systemic adverse effects, such as suppression of the hypothalamic-pituitary axis, is less than with oral prednisone therapy. Inhaled glucocorticoid formulations include fluticasone, beclomethasone, flunisolide, and triamcinolone. Currently, fluticasone is considered the most potent formulation with the longest duration of action and is the most commonly used inhaled glucocorticoid in veterinary patients.

## Ipratropium Bromide

Ipratropium bromide is a quaternary derivative of atropine that lacks its adverse effects and is available in an MDI (500 mcg/actuation), alone or in combination with albuterol. In people with asthma, ipratropium bromide is used as an additional reliever medication to reverse bronchoconstriction when inhaled short-acting  $\beta_2$ -agonists do not provide enough relief. Its anticholinergic action also decreases mucous secretions. In an experimental model of feline asthma, longterm antigen sensitization caused an augmented muscarinic receptor response to acetylcholine. Modulation of muscarinic receptors with anticholinergic drugs may be useful to treat asthmatic cats. Ipratropium has shown efficacy for recurrent airway obstruction in horses. It is not well absorbed after inhalation, so it does not cause systemic anticholinergic effects.

## Cromolyn Sodium and Nedocromil

Cromolyn sodium and nedocromil sodium are chloride-channel blockers that modulate mast cell–mediator release and eosinophil recruitment. They are both available in MDIs. Cromolyn sodium and nedocromil sodium have strong human safety profiles, but nedocromil sodium has been reported to have a broader spectrum of efficacy. In people, the clinical response to these drugs is less predictable than the response to glucocorticoids. There are no published reports of the use of cromolyn or nedocromil in asthmatic cats or dogs with bronchitis; however, pretreatment with nedocromil sodium aerosols attenuated viral-induced airway inflammation in Beagle puppies. Further investigation of these drugs in asthmatic cats seems warranted given the sensitivity of this species to serotonin released from degranulating mast cells.

## Lidocaine

Lidocaine, commonly used as a local anesthetic and antiarrhythmic agent, is used as a steroid-sparing treatment in human asthma. Initially used topically to prevent cough during bronchoscopic procedures, lidocaine, administered via nebulization, is effective for intractable cough and asthma by inhibition of eosinophil-active cytokines. Nebulization provides direct drug delivery to the lung, with minimal systemic drug absorption and few adverse effects. Nebulized lidocaine reduced airway hyperresponsiveness in experimentally asthmatic cats but did not affect airway eosinophilia, so it probably should be combined with glucocorticoids in management of feline asthma.

## Suggested Treatment Regimens

For emergency management of dyspnea in cats and dogs, 2–4 puffs of albuterol should be given every 5 min until clinical signs resolve. Additional therapy may include oxygen and an IV dose of a rapid-acting glucocorticoid.

Current recommendations for therapy of feline asthma and canine bronchitis are to use albuterol only as needed for bronchodilation and fluticasone bid. For initial therapy of moderately affected animals, a 5-day course of oral prednisone (or prednisolone) at 1 mg/kg may be helpful. Severely affected animals may require 1 mg/kg of prednisone (or prednisolone) every other day. Adjunctive therapy with other inhaled or orally administered anti-inflammatories and bronchodilators may be useful in some animals. Therapy must be individualized for each animal.

For horses with recurrent airway obstruction, environmental management and a combination of bronchodilator and anti-inflammatory therapy is recommended. Current recommendations are to use 500 mcg of albuterol every 2 hr as needed and fluticasone at 2–4 mcg/kg bid. Beclomethasone has also been used at 1–3 mcg/kg, bid, but it causes more adrenal suppression in horses than fluticasone at these doses.

# 3. Expectorants and Mucolytic Drugs

Expectorants and mucolytic drugs are used to increase the output of bronchial secretions, enhance the clearance of bronchial exudate, and promote a productive cough. Saline expectorants are promoted to stimulate bronchial mucous secretions via a vagally mediated

reflex action on the gastric mucosa. However, there are no well-designed studies that support these claims. Examples of these drugs include ammonium chloride, ammonium carbonate, potassium iodide, calcium iodide, and ethylenediamine dihydroiodide. Iodine-containing products should not be administered to pregnant, hyperthyroid, or milk-producing animals.

Direct stimulants of respiratory secretions include the volatile oils, such as eucalyptus oil and oil of lemon. They are believed to directly increase respiratory tract secretions. Their efficacy in animals is unknown.

**Guaifenesin** (glyceryl guaiacolate) is a centrally acting muscle relaxant that may also have an expectorant effect. It may stimulate bronchial secretions via vagal pathways. The volume and viscosity of bronchial secretions does not change, but particle clearance from the airways may accelerate. It is a common component of human cold remedies in combination with dextromethorphan.

**N-acetylcysteine** is available as a 10% solution that can be nebulized. Its mucolytic effect is the result of the exposed sulfhydryl groups on the compound, which interact with disulfide bonds on mucoprotein. Acetylcysteine helps to break down respiratory mucus and enhance clearance. It may also increase the levels of glutathione, which is a scavenger of oxygen-free radicals. Aerosolization of acetylcysteine can cause reflex bronchoconstriction due to irritant receptor stimulation, so its use should be preceded by bronchodilator therapy.

**Dembrexine** is a phenolic benzylamine available in some countries for respiratory disease in horses. The proposed effect is through an alteration of the constituents and viscosity of abnormal respiratory mucus and an improved efficiency of respiratory clearance mechanisms. It also has an antitussive action and enhances concentrations of antibiotics in lung secretions. It is supplied as a powder that is sprinkled on the feed at a dosage of 0.33 mg/kg, bid.

## 4. Decongestants

Decongestants are commonly used in people to treat allergic rhinitis, but they are rarely used for this purpose in animals. The  $\alpha$ -adrenergic agonist drugs cause local vasoconstriction in mucous membranes, which reduces swelling and edema. They are used topically as nasal decongestants in allergic and viral rhinitis, or systemically in combination with antihistamines as respiratory tract decongestants. Antihistamines are effective for treatment of allergic rhinitis in people when combined with the  $\alpha$ -adrenergic agonist drugs, but their effectiveness in animals has not been demonstrated. The topical  $\alpha$ -adrenergic agonist drugs act within minutes with few adverse effects, but extended use may cause rebound hyperemia and mucosal damage. Systemic administration can result in hypertension, cardiac stimulation, urinary retention, CNS stimulation, and mydriasis. Systemic administration of antihistamines often causes sedation.

## 5. Respiratory Stimulants

**Doxapram** stimulates the medullary respiratory center and the chemoreceptors of the carotid artery and aorta to increase tidal volume. Other portions of the CNS are stimulated only when high doses are administered. Doxapram is used primarily in emergency situations during anesthesia or to decrease the respiratory depressant effects of opiates and barbiturates. Recommended dosages are 1–5 mg/kg, IV, in dogs and cats, or 1–2 drops under the tongue of apneic neonates. In adult horses, the dosage is 0.5–1 mg/kg, IV, while foals are dosed carefully at 0.02–0.05 mg/kg/min, IV.

Methyloxantins (See chapter above)

# Overview of Systemic Pharmacotherapeutics of the Digestive System

## Drugs Affecting Appetite (Monogastric)

Disorders of appetite are very common in veterinary patients. Obesity from overfeeding is common in companion animals and is best managed by educating the owner and regulating the animal's diet. Anorexia is a common clinical problem seen with many systemic diseases, which exacerbates disease-induced catabolism. In the anorexic animal that does not respond to coaxing with small quantities of highly palatable foods, drug therapy may be used to stimulate appetite. The effect of specific drugs on food intake can involve hunger, satiety, or enhancement of the positive evaluation of taste.

### Appetite Suppression:

**Dirlotapide** is a microsomal triglyceride transfer protein (MTP) inhibitor developed specifically for weight loss in dogs. MTP catalyzes the assembly of triglyceride-rich apolipoprotein B-containing lipoproteins to form chylomicrons in the intestinal mucosa and very low-density lipoproteins in the liver. After oral administration, dirlotapide has in vivo selectivity for intestinal MTP. The mechanism of weight loss action is not completely understood, but dirlotapide appears to reduce fat absorption and send a satiety signal from lipid-filled enterocytes. Dirlotapide also decreases appetite in a dose-dependent manner, probably via increased release of peptide YY into the circulation. The decrease in food intake is responsible for most of the weight reduction effect.

Dirlotapide is available systemically, but absorption in dogs is highly variable. Absorbed dirlotapide is metabolized in the liver; parent drug and metabolites are secreted in the bile, with potential for enterohepatic circulation. Although blood concentrations do not directly correlate with effectiveness (effectiveness has been linked to drug concentrations in the gut), they seem to correlate with systemic toxicity.

Dirlotapide is available as a 5 mg/mL solution for oral administration. The dosage is adjusted according to the weight loss of each individual dog. The initial dosage of 0.5 mg/kg is doubled after 14 days and then adjusted monthly; the maximum permitted daily dosage is 1 mg/kg, although dosages as high as 10 mg/kg have been administered to dogs without severe adverse effects in safety studies. Dirlotapide can be used without changing the dog's current feeding or exercise regimens, but food intake should be monitored during weight stabilization to establish feeding and exercise routines that will minimize weight gain after treatment. Anorexia, emesis, and loose feces occur in some dogs. The incidence of emesis generally increases with dose and decreases with treatment time. Increases in hepatic transaminase activity were seen in dogs treated with >1.5 mg/kg/day but were not associated with clinical signs or histopathologic evidence of hepatic degeneration or necrosis.



Dirlotapide should not be used in cats. It increases the risk of hepatic lipidosis during weight loss in obese cats. Dirlotapide is not recommended for use in dogs currently receiving longterm glucocorticoid therapy or in dogs with liver disease. In people, adverse reactions associated with ingesting dirlotapide include abdominal distention, abdominal pain, diarrhea, flatulence, headache, increased serum transaminases, nausea, and vomiting.

## Appetite Stimulation:

Table

Drug	Dosage
<a href="#">Diazepam</a>	Cats: 0.005–0.4 mg/kg, IV
<a href="#">Oxazepam</a>	Cats: 2 mg, PO, bid
<a href="#">Cyproheptadine</a>	Cats: 1–4 mg, PO, bid
<a href="#">Mirtazapine</a>	Cats: 3.75 mg/cat (¼ of a 15-mg tablet), PO, every 3 days
	Dogs: ¼ of a 15-mg tablet for dogs <7 kg, ½ of a 15-mg tablet for dogs 8–15 kg, 15 mg for dogs 16–30 kg, 30 mg for dogs >30 kg; no higher than 30 mg per dog
<a href="#">Megestrol acetate</a>	Dogs: 5 mg/kg/day, PO
<a href="#">Prednisone/prednisolone</a>	1 mg/kg, PO, every other day

## Drugs Used to Stimulate Appetite

**Anabolic steroids** are synthetic derivatives of testosterone that have enhanced anabolic effects with reduced androgenic effects. Anabolic steroids do not directly affect hunger, satiety, or sensory perception of food. Instead, they antagonize the catabolic effect of glucocorticoids and the negative nitrogen balance associated with surgery, illness, trauma, and aging. In all cases, improved nitrogen balance depends on adequate protein/calorie intake and treatment of the underlying disease. Anabolic steroids stimulate hematopoiesis, appetite, and weight gain. Adverse effects of anabolic steroid therapy include hepatotoxicity, masculinization, and early closure of bony epiphyses in young animals. Anabolic steroids are contraindicated in animals with congestive heart failure because of sodium and water retention. Because of human abuse potential, anabolic steroids are controlled substances. Although once (in)famous for abuse in people and horses, stanozolol and boldenone undecylenate are no longer marketed by veterinary pharmaceutical companies in North America. Currently, any anabolic product for veterinary use can only be obtained from a compounding pharmacy. Use of anabolic steroids in performance horses is prohibited by most equine sport organizations, and detection times can be >2 mo.

**Glucocorticoids** increase gluconeogenesis and antagonize insulin for an overall hyperglycemic effect. Appetite is stimulated by the steroid-induced euphoria. Continued use of glucocorticoids has catabolic effects because skeletal muscle and collagen proteins are broken down to provide the precursors for gluconeogenesis.

When used as anxiolytics, the **benzodiazepines** (BZD) became well known for their appetite stimulation effects independent of their anxiolytic activity. Stereospecific binding of a BZD to GABA A receptors in the parabrachial nucleus produces a strong dose-dependent (ie, voracious) increase in food consumption. Hunger level and degree of satiety has no effect on BZD-induced food intake. So, it appears that the BZDs do not modulate hunger or satiety directly but act specifically to enhance taste and other sensory characteristics of food. By manipulating the stereospecificity of the BZD drugs, appetite-selective partial agonist

compounds have been developed that have actions disassociated from the other major effects of full agonists (eg, amnesia, sedation, incoordination, anxiolysis). Likewise, inverse agonists of the BZD receptors reduce food consumption. BZD receptor antagonists block the appetite-stimulating effects of the full or partial agonists, as well as the appetite-suppressive effects of the inverse agonists. So, there is a bidirectional control of food intake mediated by a common subset of BZD receptors. Levels of food intake, ranging from voracious consumption at one extreme to complete anorexia at the other, with every level in between, can be achieved by the relative concentration of agonists and inverse agonists binding to those BZD receptors specifically involved in the control of appetite. **Diazepam** is an appetite stimulant when administered IV to cats. If responsive, cats begin eating within a few seconds of IV administration, so palatable food should be available before injection. **Oxazepam**, a metabolite of diazepam, can be given orally to cats. Diazepam is the more effective appetite stimulant but also causes a greater sedative effect than oxazepam.

**Cyproheptadine** is an antihistamine with serotonin-antagonist action used clinically in cats as an appetite stimulant. It acts as a 5-HT<sub>2</sub> receptor antagonist. The lateral hypothalamus normally excretes endogenous opiates, which stimulate eating. The release of these endogenous opiates is inhibited by serotonin and cholecystokinin release, thus inhibiting eating. Cats are very sensitive to changes in serotonin concentrations, so serotonin antagonists are very potent in cats. CNS excitement and aggressive behavior may occur in some cats.

**Mirtazapine** is an antidepressant used to treat moderate to severe depression in people. Mirtazapine is not a serotonin or norepinephrine reuptake inhibitor (SSRIs such as fluoxetine are noted to decrease appetite). It is an antagonist of presynaptic  $\alpha_2$ -adrenergic autoreceptors and heteroreceptors on both norepinephrine and serotonin (5-HT) presynaptic axons, plus is a potent antagonist of postsynaptic 5-HT<sub>2</sub> and 5-HT<sub>3</sub> receptors. This mechanism of action maintains equivalent antidepressant efficacy but minimizes many of the adverse effects common to both tricyclic antidepressants and SSRIs. Because of its unique pharmacologic profile, mirtazapine usually does not cause anticholinergic effects, serotonin-related adverse effects, or adrenergic adverse effects (orthostatic hypotension and sexual dysfunction). Antihistaminic drowsiness is a common effect. Mirtazapine is used for disease conditions in which inappetence and nausea go together, such as in the treatment of GI disease or liver or kidney disease. Mirtazapine can also be used to alleviate the nausea and appetite loss that accompanies chemotherapy.  $\alpha$ -Adrenergic receptors in the chemoreceptor trigger zone are important in inducing emesis in cats. Clinically, mirtazapine is an effective appetite stimulant and antiemetic for cats with chronic kidney disease and appears to be a useful adjunct in nutritional management of these cats. There is little pharmacokinetic information on mirtazapine in dogs and cats, but mirtazapine shows sexual effects in hepatic metabolism in people, so it is likely there is similar variation in metabolism in dogs and cats and the potential for variation in efficacy.

Mirtazapine is typically given once a day to dogs and twice a week to cats. It should be used with caution in dogs and cats with severe liver or kidney disease, because mirtazapine clearance will be reduced. In cats and small dogs, it is difficult to reduce the dose, because the smallest tablet manufactured cannot be accurately cut much smaller than the regular dosing schedule allows. In this situation, a compounding pharmacy could be employed to create a lower dose, or the dosing schedule can be extended. This is especially important for cats with liver disease.

**Megestrol acetate** is a synthetic progestin. It has significant antiestrogen and glucocorticoid activity, with resulting adrenal suppression. It is used to stimulate appetite and promote weight gain in people with cancer and cachexia (related to acquired immunodeficiency syndrome) and may have a similar effect in anorectic cats and dogs. Megestrol acetate is contraindicated in pregnant animals and in animals with uterine disease, diabetes mellitus, or mammary neoplasia. In cats, megestrol acetate can induce a profound adrenocortical suppression, adrenal atrophy, and diabetes mellitus, which may or may not be reversible. Toxicity is less of a problem in dogs.

Other drugs used as appetite stimulants include **B vitamins** and **glucocorticoids**. B vitamin preparations are administered orally and parenterally to debilitated animals, especially horses, to promote appetite. Glucocorticoids increase gluconeogenesis and antagonize insulin for an overall hyperglycemic effect. Appetite is stimulated by the steroid-induced euphoria. Continued use of glucocorticoids results in catabolic effects, as skeletal muscle and collagen proteins are broken down to provide the precursors for gluconeogenesis.

## Drugs to Control or Stimulate Vomiting (Monogastric)

Animals possess an arsenal of special abilities for survival, many of which are used for food consumption. Ingesting food can lead to exposure of internal organs to possible food-related disorders, including viral and bacterial infection, toxins, and allergens. Smell and taste are not always effective in determining the quality of food, so nausea, vomiting, and diarrhea are additional mechanisms of defense of the GI system.

Humorally mediated emesis results from emetogenic substances in the systemic circulation that activate the chemoreceptor trigger zone (CRTZ) in the area postrema. The CRTZ lies outside the blood-brain barrier. Neurally mediated emesis results from activation of an afferent neural pathway typically coming from the abdominal viscera and synapsing at one or more nuclei in the emetic center. Most pharmacologic interventions focus on the humoral pathway of emesis, based on neurotransmitter interactions at the CRTZ. The neural pathway has received less emphasis, even though it is a much more important pathway.

Nausea is an aversive experience that often accompanies emesis; it is a distinct perception, different from pain or stress. Nausea is more difficult to treat than emesis using antiemetic drugs. This became apparent with the excellent control of drug-induced emesis from cancer chemotherapy, but human patients still experience nausea. This suggests that nausea and vomiting are separate physiologic processes.

Motion-induced emesis appears to have a very early evolutionary origin, because it is present in most animal models of emesis. Motion sickness is thought to result from sensory conflict regarding the body's position in space, yet there is no satisfactory theory as to why people and animals have this mechanism in the first place.

Nausea and vomiting, as defense systems of the GI tract, by necessity must have a low threshold for activation. Cats are well known for their tendency to vomit, particularly when attempting to dislodge hairballs from the throat or upper GI tract. Chronic vomiting in cats

may indicate underlying thyroid, liver, or kidney dysfunction and should be investigated. Dogs also vomit often (frequently after eating grass) and often eat their own vomit.

## Neurotransmitters of Emesis:

Acetylcholine (muscarinic receptors) and substance P (NK-1 receptors) act on the emetic center. The CRTZ is stimulated by dopamine (D2 receptors),  $\alpha_2$ -adrenergic drugs (NE receptors), serotonin (5-HT<sub>3</sub> receptors), acetylcholine (M1 receptors), enkephalins, and histamine (H1 and H2 receptors).

$\alpha$ -Adrenergic receptors in the CRTZ are important in inducing emesis in cats.  $\alpha_2$ -Adrenergic agonists (eg, xylazine) are more potent emetics in cats than in dogs.

5-HT<sub>1A</sub> antagonists (eg, buspirone) and  $\alpha_2$ -adrenergic antagonists (eg, acepromazine, yohimbine, mirtazapine) suppress vomiting in cats.

CRTZ D2 dopamine receptors are not as important in mediating humoral emesis in cats as they are in dogs. Apomorphine, a D2 dopamine receptor agonist is a more reliable emetic in dogs than cats, and D2 dopamine receptor antagonists (eg, metoclopramide) are not very effective antiemetic drugs in cats.

Histamine H1 and H2 receptors are found in the CRTZ of dogs but not cats. Histamine is a potent emetic in dogs but not cats, and H1 antagonists (eg, diphenhydramine) are ineffective for motion sickness in cats.

Muscarinic M1 receptors are found in the vestibular apparatus of cats. Mixed M1/M2 antagonists (eg, atropine) inhibit motion sickness in cats.

Substance P binds to NK-1 receptors, which are found in the gut and the emetic center of the CNS. Substance P induces emesis, and selective substance P antagonists (eg, maropitant) are potent antiemetics in both dogs and cats with a broad spectrum of activity against a variety of emetic stimuli.

## Emetic Drugs:

Emetic drugs are usually administered in emergency situations after ingestion of a toxin (see Emetic Drugs). They generally remove <80% of the stomach contents. The most reliable emetic drugs act centrally to stimulate the vomiting center, either directly or via the CRTZ.

Table

Drug	Dosage
<a href="#">Apomorphine</a>	Dogs: 4 mg/kg, PO; 0.02 mg/kg, IV; 0.3 mg/kg, SC; 0.25 mg in the conjunctival sac
Xylazine	Cats: 0.4–0.5 mg/kg, IV or IM
Hydrogen peroxide	Dogs: 5–10 mL, PO

Emetic Drugs

**Apomorphine** is an opioid drug that acts as a potent central dopamine agonist to directly stimulate the CRTZ. Therefore, it is less effective in cats than in dogs. It can be administered PO, IV, or SC; the IM route is not as effective. It can also be applied directly to conjunctival and gingival membranes, using the tablet formulation, which can easily be removed once emesis is initiated. Vomiting usually occurs in 5–10 min. Although apomorphine directly stimulates the CRTZ, it has a depressant effect on the emetic center. Therefore, if the first dose does not induce emesis, additional doses are not helpful. Because the vestibular apparatus may also be involved in apomorphine-induced vomiting, sedate and motionless animals will not vomit as readily as active animals. Excitement that results from apomorphine in cats can be treated with the opioid antagonist naloxone.

**Xylazine** is an  $\alpha_2$ -adrenergic agonist used primarily for its sedative and analgesic action. It is a reliable emetic, particularly in cats, in which it stimulates the CRTZ. Because xylazine can produce profound sedation and hypotension, animals should be closely monitored after administration.

**Hydrogen peroxide** (3%) applied to the back of the pharynx stimulates vomiting via the ninth cranial nerve. Small doses (5–10 mL) of hydrogen peroxide can be administered via oral syringe until emesis occurs. It should be administered cautiously, especially in cats, because aspiration of hydrogen peroxide foam causes severe aspiration pneumonia. When small amounts are administered, 3% hydrogen peroxide is relatively nontoxic. Stronger concentrations (eg, hair dye peroxide) are more toxic.

Other products have been used but are not recommended to induce emesis in dogs and cats. **Syrup of ipecac** is no longer recommended for "home use" in people or animals. The active ingredient is emetine, a toxic alkaloid, which produces vomiting by acting as a stomach irritant. If repeated use fails to induce emesis, then gastric lavage is necessary to remove the emetine to prevent additional toxicosis. Although sometimes suggested, **sodium chloride (salt)** and **powdered mustard** should not be used. Mustard is rarely effective and can be inhaled and cause lung damage, whereas salt toxicity can easily occur if overdosed and can result in fatal cerebral edema.

### Antiemetic Drugs:

Protracted vomiting is physically exhausting and can cause dehydration, acid-base and electrolyte disturbances, and aspiration pneumonia. Antiemetic drugs are used to control excessive vomiting once an etiologic diagnosis has been made, to prevent motion sickness and psychogenic vomiting, and to control emesis from radiation and chemotherapy (see Antiemetic Drugs). Antiemetics may act peripherally to reduce afferent input from receptors or to inhibit efferent components of the vomiting reflex response. They may also act centrally to block stimulation of the CRTZ and emetic center.

Table

Drug	Dosage
Acepromazine	0.025–0.2 mg/kg, IV, IM, SC, maximum 3 mg; 1–3 mg/kg, PO
<a href="#">Chlorpromazine</a>	0.5 mg/kg, IV, IM, SC, tid-qid
<a href="#">Prochlorperazine</a>	0.1 mg/kg, IM, tid-qid; 1 mg/kg, PO, bid
Aminopentamide	0.022 mg/kg, PO, SC, or IM, bid-tid
<a href="#">Dimenhydrinate</a>	4–8 mg/kg, PO, tid
<a href="#">Diphenhydramine</a>	2–4 mg/kg, PO, tid
<a href="#">Butorphanol</a>	0.2–0.4 mg/kg, IM, once to twice daily
<a href="#">Metoclopramide</a>	0.1–0.5 mg/kg, IM, SC, or PO, tid; 0.01–0.02 mg/kg/hr, IV infusion
<a href="#">Ondansetron</a>	0.1–0.2 mg/kg, PO, once to twice daily; 0.1–0.15 mg/kg, IV, bid-tid
<a href="#">Granisetron</a>	0.5–1 mg/kg, PO, bid; 0.1–0.15 mg/kg, IV, bid-tid
<a href="#">Dolasetron</a>	0.6–1 mg/kg/day, IV
Maropitant	2 mg/kg, PO or 1 mg/kg/day, SC, for up to 5 days (acute vomiting); 8 mg/kg/day, PO, for up to 2 days (motion sickness)

## Antiemetic Drugs

The **phenothiazine tranquilizers** are  $\alpha_2$ -adrenergic antagonists and antagonize the CNS stimulatory effects of dopamine and decrease vomiting from a variety of causes, including motion sickness in cats. These drugs also have antihistaminic and weak anticholinergic action. Phenothiazine tranquilizers used as antiemetics include acepromazine, chlorpromazine, and prochlorperazine. Potential adverse effects include hypotension due to  $\alpha$ -adrenergic blockade, excessive sedation, extrapyramidal signs, and a lowering of the seizure threshold in animals with epilepsy. Extrapyramidal signs can be counteracted with an antihistamine (eg, diphenhydramine).

The **anticholinergic drugs** block cholinergic afferent pathways from the GI tract and the vestibular system to the vomiting center. Alone, they are less effective than the other emetics. Aminopentamide is approved for use in dogs and cats in the USA as an injectable formulation and oral tablets. It should be more efficacious in the treatment of motion sickness in cats than in dogs, because muscarinic M1 receptors are found in the vestibular apparatus of cats. Aminopentamide has low efficacy for other causes of vomiting.

The **antihistamines** can block both cholinergic and histaminic nerve transmission responsible for transmission of the vestibular stimulus to the vomiting center of dogs. The commonly used histamine (H1) blocking drugs are diphenhydramine and dimenhydrinate (diphenhydramine plus 8-chlorotheophylline). They may cause mild sedation, especially diphenhydramine, but paradoxical CNS stimulation may also occur, presumably from anticholinergic effects.

**Metoclopramide** exerts its antiemetic effects via three mechanisms. At low doses, it inhibits dopaminergic transmission in the CNS, whereas at high doses, it inhibits serotonin receptors in the CRTZ. Peripherally, metoclopramide increases gastric and upper duodenal emptying. Metoclopramide is a useful antiemetic for dogs. Because CRTZ D2 dopamine receptors are not very important in mediating humoral emesis in cats, metoclopramide is less effective in cats than in dogs. It is used to control emesis induced by chemotherapy, nausea and vomiting associated with delayed gastric emptying, reflux gastritis, and viral enteritis. There is tremendous individual variability in metoclopramide pharmacokinetics, and oral



bioavailability is only ~50% because of a significant first-pass effect. At high doses or with rapid IV administration, metoclopramide causes CNS excitement by dopamine antagonism (similar to the phenothiazine tranquilizers). Extrapyramidal signs can be counteracted with an antihistamine such as diphenhydramine. Metoclopramide should not be administered if a GI obstruction or perforation is suspected.

The **serotonin antagonists** ondansetron, granisetron, and dolasetron are specific inhibitors of serotonin subtype 3 receptors in the CRTZ. These receptors are located peripherally on vagal nerve terminals and centrally in the area postrema of the brain. Cytotoxic drugs and radiation damage the GI mucosa, causing release of serotonin. These are the most effective antiemetics used in people undergoing radiation and chemotherapy, and they have been used in cats and dogs receiving chemotherapy. Although very effective at controlling vomiting associated with chemotherapy and drug-induced vomiting, these drugs do not prevent or relieve nausea, which may be more debilitating than vomiting. They are not effective for emesis caused by motion sickness. All serotonin subtype 3 antagonists have been associated with prolongation of the QT interval in people. Adverse effects of dolasetron include ECG changes (PR and QT prolongation, QRS widening) caused by dolasetron metabolites that block sodium channels.

**Butorphanol** is an effective antiemetic for dogs receiving cisplatin chemotherapy. It causes only mild sedation. It is believed to exert its antiemetic effect directly on the vomiting center.

**Maropitant** is a neurokinin 1 (NK-1) receptor antagonist approved to treat and prevent emesis in dogs and cats. Substance P is a regulatory peptide that binds to the NK-1 receptors and induces emesis. NK-1 receptor antagonists are believed to provide antiemetic activity by suppressing activity at the nucleus of the solitary tract, where vagal afferents from the GI tract converge with inputs from the CRTZ and other regions of the brain involved in the control and initiation of emesis. Despite its selectivity for the NK-1 receptor, maropitant blocks apomorphine, cisplatin, and syrup of ipecac-induced vomiting in dogs, which suggests that activation of the nucleus of the solitary tract is a final common step in the initiation of emesis. Despite being very effective antiemetics in people, NK-1 receptor antagonists have little effect on chemotherapy-associated nausea in people or hydromorphone-induced nausea in dogs.

Maropitant injectable is approved for vomiting in cats  $\geq 16$  wk old and acute vomiting in dogs  $\geq 8$  wk old at 1 mg/kg/day. Maropitant tablets are approved for acute vomiting in dogs  $\geq 8$  wk old (2 mg/kg), and to prevent vomiting due to motion sickness in dogs  $\geq 16$  wk older (8 mg/kg). Dogs should not be fed for 1 hr before giving maropitant. The best time to give maropitant is 2 hr before travelling, with a small amount of food. The tablets should not be wrapped tightly in fatty food such as cheese or meat, because this may keep the tablets from dissolving and delay the effect of maropitant.

Adverse effects are rare with maropitant, but the most common ones are excessive drooling, lethargy, lack of appetite, and diarrhea. Maropitant injections may also cause a stinging sensation; this can be minimized by keeping the injectable solution refrigerated and, once the drug is drawn up, injecting right away at the refrigerated temperature. A few dogs may vomit after treatment. Giving maropitant with a small amount of food will help avoid this.

# Therapy of Gastrointestinal Ulcers (Monogastric)

GI ulceration is a common problem in small and large animals, in association with physiologic stress (endogenous cortisol), dietary management, or as a sequela of administration of ulcerogenic drugs. *Helicobacter* organisms, the most frequent cause of ulcers in people, appear to be involved in some cases of gastritis in animals. Antiulcerative drugs include antagonists that interact with stimulatory receptors (histamine H<sub>2</sub>-receptor antagonists, muscarinic receptor antagonists, and gastrin receptor antagonists), agonists that interact with inhibitory receptors (somatostatin and prostaglandin E analogues), and irreversible inhibitors of H<sup>+</sup>/K<sup>+</sup>-ATPase (proton pump inhibitors). Antiulcerative drugs are listed in Antiulcerative Drugs.

Table

Drug	Dosage
Antacids	2–10 mL, PO, every 2–4 hr
<a href="#">Sucralfate</a>	Cats: 250 mg, bid-tid
	Dogs: 500 mg to 1 g, tid-qid
	Foals: 1–2 g, qid
<a href="#">Cimetidine</a>	Dogs: 5–10 mg/kg, PO, qid
	Horses: 4 mg/kg, IV, bid; 18 mg/kg, PO, bid
<a href="#">Ranitidine</a>	Dogs: 0.5 mg/kg, PO, SC, or IV, bid
	Horses: 1.3 mg/kg, IV, bid; 11 mg/kg, PO, bid
<a href="#">Famotidine</a>	Dogs: 0.5–1 mg/kg/day, PO or IV
	Horses: 0.4 mg/kg, IV, bid; 3 mg/kg, PO, bid
<a href="#">Omeprazole</a>	Dogs: 0.5–1 mg/kg/day, PO
	Horses: 4 mg/kg/day, PO, for treatment; 2 mg/kg/day, PO, to prevent recurrence
<a href="#">Misoprostol</a>	Dogs: 2–5 mcg/kg, PO, tid-qid

## Antiulcerative Drugs

### Antacids:

The common antacids are bases of aluminum, magnesium, or calcium (aluminum hydroxide, magnesium oxide or hydroxide, and calcium carbonate). These drugs neutralize stomach acid to form water and a neutral salt. They are usually not absorbed systemically. In addition to their acid-neutralizing ability, antacids decrease pepsin activity, binding to bile acids in the

stomach and stimulating local prostaglandin (PGE<sub>1</sub>) production. Over-the-counter antacid preparations are combinations of magnesium hydroxide and aluminum hydroxide; such combinations optimize the buffering capabilities of each compound and balance the constipating effect (from aluminum hydroxide) and the laxative effect (from magnesium hydroxide). Up to 20% of the magnesium can be absorbed after administration PO and can cause hypermagnesemia in animals with renal insufficiency. Antacids frequently interfere with the GI absorption of concurrently administered drugs (eg, digoxin, tetracyclines, fluoroquinolones). Aluminum-containing antacids impair absorption of phosphate. Because they are difficult to administer and require frequent dosing, they are not as popular as newer therapies.

### Sucralfate:

Sucralfate is an antiulcerative drug that has a cytoprotective effect on GI mucosa. It disassociates in the acid environment of the stomach to sucrose octasulfate and aluminum hydroxide. Sucrose octasulfate polymerizes to a viscous, sticky substance that creates a protective effect by binding to ulcerated mucosa. This prevents “back diffusion” of hydrogen ions, inactivates pepsin, and adsorbs bile acid. In addition, sucralfate increases the mucosal synthesis of prostaglandins, which have a cytoprotective role. Because sucralfate is not absorbed, it causes virtually no adverse effects. Dosage regimens are extrapolated from human dosages. Although sucralfate is frequently administered to horses and small animals as an ulcer preventive, there is little evidence of efficacy in animals, and it may prevent the absorption of truly useful drugs. Animals in renal failure may have increased aluminum absorption.

### H<sub>2</sub>-Receptor Antagonists:

**Cimetidine**, **ranitidine**, and **famotidine** are the commonly used H<sub>2</sub>-receptor antagonists. Ranitidine is 3–13 times as potent on a molar basis as cimetidine in inhibiting gastric acid secretion. Famotidine is 20–150 times as potent as cimetidine. In people, food tends to delay the absorption of cimetidine, has minimal effect on ranitidine, and slightly enhances absorption of famotidine. Some evidence suggests that cimetidine strengthens the gastric mucosal defenses against ulceration and enhances cytoprotection. Cimetidine reduces the metabolism of other drugs (warfarin, phenytoin, lidocaine, metronidazole, theophylline) by inhibiting hepatic microsomal enzyme systems. Ranitidine interacts differently than cimetidine and only minimally (10%) inhibits hepatic metabolism of some drugs. Famotidine seems to have no effect on metabolism of other drugs. Antacids should be given 1 hr before or after cimetidine to avoid interactions. Famotidine may be given with antacids; ranitidine may be given with low doses of antacids. Sucralfate may alter absorption of cimetidine and ranitidine.

Cimetidine suppresses gastric acid secretion in dogs for 3–5 hr. Because ranitidine has a longer elimination half-life, it suppresses acid for up to 8 hr and it may be administered less frequently. Famotidine can be administered once a day. Oral bioavailability in horses for these drugs is only 10%–30%, so large oral doses must be administered.

## Proton Pump Inhibitors:

Proton pump inhibitors (PPIs) irreversibly block the  $H^+/K^+$ -ATPase proton pump of the gastric parietal cell. They are given in an inactive form, which is neutrally charged (lipophilic) and readily crosses cell membranes into intracellular compartments (like the parietal cell canaliculus) that have acidic environments. The inactive drug is protonated, rearranges into its active form, and irreversibly binds to and deactivates the proton pump. The most widely used PPI is **omeprazole**. In dogs and horses, a single dose of omeprazole inhibits acid secretion for 3–4 days, despite a relatively short plasma half-life. This is because of accumulation of the drug in parietal cell canaliculi and the irreversible nature of proton pump inhibition.

A specific equine product has been developed, because oral bioavailability of the human omeprazole formulation or compounded formulations is poor in horses. Although ulcers in horses will heal while on omeprazole therapy, they tend to recur once therapy is discontinued. Human formulations are used in dogs and cats. In people, adverse effects from suppression of gastric acid secretion include hypergastrinemia, which causes mucosal cell hyperplasia, hypertrophy of the gastric rugae, and eventually development of carcinoids. It has also been associated with acute renal failure and disorders of calcium homeostasis, including fractures associated with longterm use. Studies in rodents show that PPIs can exacerbate NSAID-induced intestinal damage from significant shifts in enteric microbial populations. Prevention or reversal of this dysbiosis may be an important clinical consideration for reducing the incidence and severity of NSAID enteropathy. Therefore, omeprazole is contraindicated for chronic therapy. Omeprazole is also a microsomal enzyme inhibitor (to a similar extent as cimetidine). For animals that cannot receive oral medications, IV injectable formulations approved for people (pantoprazole and esomeprazole) can be considered for use.

## Acid Rebound:

Acid rebound is an increase in gastric acid secretion above pretreatment levels after discontinuation of antiulcer therapy. Rebound is reported after the use of histamine  $H_2$ -receptor antagonists and PPIs and is thought to be due to increased serum gastrin and/or upregulation of the  $H_2$ -receptors. An increased gastrin level, or hypergastrinemia, is a secondary effect that occurs during chronic inhibition of gastric acid secretion, such as with longterm antiulcer therapy. Gastrin is the primary regulator of gastric acid secretion, which is mediated by histamine released by the enterochromaffin-like (ECL) cell. Increased plasma gastrin stimulates and upregulates ECL cells to produce and release more histamine to stimulate parietal cells. In addition, an increase in parietal cell mass may occur with the chronic use of  $H_2$ -blockers or PPIs, and this may be an additional mechanism for increased acid secretion that occurs after discontinuation of therapy.

## Misoprostol:

Misoprostol is a synthetic prostaglandin  $E_1$  analogue used in dogs to reduce the risk of GI ulcers induced by chronic NSAID therapy. Misoprostol suppresses gastric acid secretion by inhibiting the activation of histamine-sensitive adenylate cyclase. It has a cytoprotective effect from stimulation of bicarbonate and mucus secretion, increased mucosal blood flow, decreased vascular permeability, and increased cellular proliferation and migration.

Misoprostol is clinically effective in preventing GI bleeding and ulceration from NSAID therapy but not from methylprednisolone sodium succinate, and it is less efficacious than  $H_2$ -receptor antagonists or PPIs for treatment of ulcers. Adverse effects of misoprostol are mainly

limited to diarrhea and flatulence. Magnesium-containing antacids may aggravate the diarrhea. Misoprostol is contraindicated in pregnant dogs, because it can induce abortion.

## Drugs Used in Treatment of Diarrhea (Monogastric)

Therapy for diarrhea in dogs, cats, horses and other non-ruminants includes fluids, electrolyte replacement, maintenance of acid/base balance, and control of discomfort. Antiparasitic drugs or dietary therapy can also play an important role in treatment of some types of diarrhea. Additional therapy may include intestinal protectants, motility modifiers, antimicrobials, anti-inflammatory drugs, and antitoxins

Table

Drug	Dosage
Kaolin-pectin	1–2 mL/kg, PO, qid
Activated charcoal	2–8 g/kg, PO
Bismuth subsalicylate	1–3 mL/kg/day in divided doses, PO
Aminopentamide	0.1–0.4 mg, IM, SC, or PO, bid
Isopropamide	0.2–1 mg/kg, PO, bid
<a href="#">Propantheline</a>	0.25–0.5 mg/kg, PO, bid-tid
<a href="#">Paregoric</a>	0.06 mg/kg, PO, tid
Diphenoxylate	0.05–0.1 mg/kg, PO, qid
<a href="#">Loperamide</a>	0.08 mg/kg, PO, tid-qid

### Antidiarrheal Drugs

#### Mucosal Protectants and Adsorbents:

**Kaolin-pectin** formulations are popular for symptomatic therapy of diarrhea. Kaolin is a form of aluminum silicate, and pectin is a carbohydrate extracted from the rind of citrus fruits. The manufacturers claim that kaolin-pectin acts as a demulcent and adsorbent in the treatment of diarrhea. This action is claimed to be related to the binding of bacterial toxins (endotoxins and enterotoxins) in the GI tract. However, clinical studies have not demonstrated any benefit from administration of kaolin-pectin. It may change the consistency of the feces but neither decreases the fluid or electrolyte loss nor shortens the duration of illness. Nevertheless, it is often administered to small animals, foals, calves, lambs, and kids. Kaolin-pectin products may adsorb or bind other drugs administered PO and reduce bioavailability.

**Activated charcoal** is derived from wood, peat, coconut, or pecan shells. The material is heated and treated in such a way that many large pores are formed, which dramatically increases the internal surface area. Activated charcoal is available in a variety of pore sizes. The formulations sold for drug and toxicant adsorption typically have pore sizes of 10–20 Å. Activated charcoal is very effective for adsorbing bacterial enterotoxins and endotoxins that cause some types of diarrhea. It also adsorbs many drugs and toxins and prevents GI absorption, so it is a common nonspecific treatment for intoxications. Activated charcoal is not absorbed, so overdose is not a problem.

Although other “mucosal protectants” have questionable efficacy, **bismuth subsalicylate** is considered by many human gastroenterologists to be the symptomatic treatment of choice for acute diarrhea. Its efficacy has been proved in controlled clinical trials in people with acute diarrhea (enterotoxigenic *Escherichia coli* or “traveller’s diarrhea”). Bismuth adsorbs bacterial enterotoxins and endotoxins and has a GI protective effect. The salicylate component has antiprostaglandin activity. Practically all of the salicylate is absorbed systemically when administered to dogs and cats. Some animals may dislike the taste of bismuth subsalicylate, and owners should be warned that it will turn the feces black. This may interfere with evaluating the feces for hemorrhage. Salicylate toxicosis is possible, especially in cats.

### Motility-modifying Drugs:

**Anticholinergic drugs** are common ingredients in antidiarrheal preparations, because they significantly decrease intestinal motility and secretions. Their parasympatholytic effects decrease segmental and propulsive intestinal smooth muscle contractions and relax spasms of smooth muscle. Although they do not alter the course of the disease, anticholinergic drugs decrease the urgency associated with some forms of diarrhea in small animals, the amount of fluid secreted into the intestine, and abdominal cramping associated with hypermotility. Because few of the types of diarrhea seen in animals can be classified as “hypermotile,” use of anticholinergic drugs is limited in veterinary medicine. Intestinal motility is already impaired in many animals with diarrhea, and these drugs may actually worsen the diarrhea. The anticholinergic drugs also have profound systemic pharmacologic effects. If they are administered in sufficient doses to affect intestinal motility, possible adverse effects include severe ileus, xerostomia, urine retention, cycloplegia, tachycardia, and CNS excitement. Chronic administration may lead to serious intestinal atony.

Atropine is the best known anticholinergic drug, but because it has many other systemic effects, it is not ordinarily used for an antidiarrheal effect. To avoid CNS excitement, quaternary amines such as aminopentamide, isopropamide, and propantheline are preferred, because they do not cross the blood-brain barrier readily.

Hyoscine butylbromide is an antispasmodic and anticholinergic drug that relaxes the smooth muscle of the GI tract. It is approved for treatment of uncomplicated, spasmodic colic in horses. Initial relief of colic pain is seen within 5–10 minutes, with a duration of action of 3–4 hr. Because of its parasympatholytic effects, it causes transient tachycardia; therefore, heart rate monitoring is not an effective indicator of response to treatment for up to 30 min after treatment. It will also decrease gut sounds for 30 min after administration. Rectal relaxation will also make rectal palpation easier. It may also be beneficial in cases of choke, and it will relieve acute bronchoconstriction in horses with recurrent airway obstruction. Hyoscine butylbromide can be administered concurrently with NSAIDs and sedatives.



**Opiates** have both antisecretory and antimotility effects by action on the  $\mu$  (mu) and  $\delta$  (delta) receptors of the GI tract. They decrease propulsive intestinal contractions and increase segmentation for an overall constipating effect. They also increase GI sphincter tone. There is some evidence that opiates inhibit colonic motor activity in horses. In addition to affecting motility, opiates stimulate absorption of fluid, electrolytes, and glucose. Their effects on secretory diarrhea are probably related to inhibition of calcium influx and decreased calmodulin activity. They are frequently used for treatment of diarrhea in dogs, but their use in cats is controversial because they may cause excitement. The constipating effects of morphine and codeine have been known for many years, but they are not used clinically as antidiarrheal drugs. Paregoric is a tincture of opium product and a controlled substance (5 mL of paregoric corresponds to ~2 mg of morphine). Diphenoxylate and loperamide are two synthetic opiates that have specific action on the GI tract without causing other systemic effects. They have been used in small animals and large animal neonates. Diphenoxylate is a controlled substance in a formulation that contains atropine to discourage abuse; at therapeutic doses, there is no effect from the atropine. Opiates can have potent effects on the GI tract and should be used cautiously. Loperamide is available over-the-counter.

Loperamide should not be used in dog breeds known to be sensitive to ivermectin (Collies, Australian Shepherds, Old English Sheepdogs) without genetic testing. These dogs may have a gene mutation (ABCB-1 gene deletion) that causes a functional defect in P-glycoprotein, which controls drug movement in many tissues. In people and genetically normal dogs, large doses of loperamide do not cause the typical CNS effects of opioids, because loperamide does not achieve high concentrations within the CNS because of P-glycoprotein-mediated efflux of loperamide. Dogs with the ABCB-1 gene deletion show signs of ptialism, panting, ataxia, and recumbency at doses of loperamide that do not affect healthy dogs. These drugs are contraindicated in infectious diarrhea, because slowing GI transit time may increase the absorption of bacterial toxins. In dogs, constipation and bloat are the most common adverse effects. Potentially, paralytic ileus, toxic megacolon, pancreatitis, and CNS effects can develop, especially in cats.

### Antimicrobial Therapy:

The efficacy of antimicrobials in the therapy of diarrhea is unknown or unproved in most clinical situations. In most cases of diarrhea in small animals, a bacterial etiology is not identified. In large animals, antimicrobial therapy has not been shown to alter the course of bacterial enteritis, and in some cases, is thought to perpetuate the disease by producing “carrier” animals (eg, salmonellosis). Nonabsorbed antimicrobials are frequently combined with motility modifiers, adsorbents, and intestinal protectants in some preparations. Many of these combinations are irrational. Antimicrobials frequently are a treatment for diarrhea in animals, but there are few conditions that have a known etiology for which antimicrobial therapy is indicated. *Campylobacter* enteritis, from infection with *Campylobacter jejuni*, is seen in cats and dogs and can be zoonotic. Treatment alleviates clinical signs, but animals usually remain carriers. Suggested antimicrobial therapy includes erythromycin, enrofloxacin, clindamycin, tylosin, tetracycline, or chloramphenicol. Intestinal bacterial overgrowth is usually due to *Escherichia coli* or *Clostridium* spp, so therapy is initiated with an oral drug effective in the GI lumen with anaerobic activity (eg, metronidazole, amoxicillin, ampicillin, tylosin, or clindamycin). Equine monocytic ehrlichiosis is caused by the rickettsial organism *Neorickettsia (Ehrlichia) risticii* but clinically resembles salmonellosis. Treatment of choice is IV oxytetracycline. Oral doxycycline can be used in mildly affected horses.

Enteritis from a variety of pathogens is common in young animals. When integrity of the intestinal mucosa is lost, septicemia or endotoxemia is likely. Signs of sepsis include severe bloody diarrhea, fever, scleral injection, dehydration, and alteration in the leukogram (early leukopenia in endotoxic shock, followed by leukocytosis). If septicemia or endotoxemia is suspected, systemic antimicrobials are warranted along with NSAIDs. Neonates with diarrhea deteriorate rapidly before culture and sensitivity results are available. Therefore, broad-spectrum antimicrobial therapy should be initiated. Suggested antimicrobials (depending on species) include fluoroquinolones, a penicillin or cephalosporin plus an aminoglycoside (gentamicin, amikacin), ampicillin or amoxicillin, tetracyclines, potentiated sulfonamides, chloramphenicol, or florfenicol. In septic animals, GI absorption is likely to be altered, so parenteral administration is preferred.

### **Nonsteroidal Anti-inflammatory Drugs (NSAIDs):**

The antiprostaglandin activity of NSAIDs may be beneficial with some types of diarrhea and may be important in treatment of septicemia or endotoxemia. Prostaglandins are important intracellular messengers for stimulating hypersecretion by the intestinal mucosa, possibly by stimulating an increase in cAMP. Antiprostaglandin drugs may directly inhibit fluid and electrolyte hypersecretion by the intestinal cells. NSAIDs should be administered cautiously, because they have adverse GI, hepatic, and renal effects.

## **Drugs Used in Treatment of Chronic Colitis (Monogastric)**

The specific cause of chronic colitis in animals is frequently unknown; therefore, it is difficult to prescribe a specific treatment for the underlying disorder. Colitis is often classified as plasmacytic/lymphocytic, eosinophilic, histiocytic, or granulomatous. The goal of colitis therapy is to restore normal intestinal motility and to relieve inflammation, spasm, or ulceration. In small animals, dietary therapy is a major component of therapy for chronic colitis

Table

Drug	Dosage
<a href="#">Sulfasalazine</a>	10–30 mg/kg, PO, bid-tid
Tylosin	40–80 mg/kg/day
<a href="#">Metronidazole</a>	10–30 mg/kg, PO, once to three times daily
<a href="#">Prednisone</a>	2–4 mg/kg, PO, every other day
<a href="#">Budesonide</a>	3 mg/m <sup>2</sup> /day, PO
Raw linseed oil	1 oz/day in the feed
<a href="#">Azathioprine</a>	50 mg/m <sup>2</sup> , PO, daily for 2 wk, then every other day
<a href="#">Chlorambucil</a>	2 mg/m <sup>2</sup> , PO, every other day

#### Drugs Used for Chronic Colitis

**Sulfasalazine** is composed of sulfapyridine and 5-aminosalicylic acid (mesalamine) joined by an azo bond. The bond is broken by bacteria in the colon to release the two drugs. The sulfonamide component is absorbed into the circulation, whereas the salicylic acid component is active locally in the GI tract. Less than half of the salicylate component is absorbed systemically. Clinical efficacy appears to be primarily due to the anti-inflammatory effect of the salicylate component. There is evidence for antilipoxygenase activity, decreased interleukin-1, decreased prostaglandin synthesis, and oxygen radical scavenging activity. Sulfasalazine is commonly used in small animals in the therapy of ulcerative or idiopathic colitis or of plasmacytic-lymphocytic colitis once dietary causes have been excluded.

Because the salicylate component is only minimally absorbed, its systemic effects are minimal. The sulfonamide component may cause keratoconjunctivitis sicca in dogs, and the salicylate component may cause toxicity in cats. Dosage recommendations for sulfasalazine vary widely, and the dosage is gradually reduced after an initial response. New products have been developed to overcome the difficulty of the 5-aminosalicylic acid reaching the colon and the systemic adverse effects. Mesalamine is a pH-sensitive, coated 5-aminosalicylic acid. The polymer coating prevents release of the active drug until it reaches the colon. Olsalazine consists of two molecules of 5-aminosalicylic acid joined together by an azo bond. Mesalamine is also available as an enema. Rectal administration allows delivery of active drug to the colon. It appears useful in dogs with chemotherapy-induced hemorrhagic colitis or with idiopathic distal proctitis. It may also be useful in dogs with perianal fistulas.

**Tylosin** is a macrolide antimicrobial used successfully in some animals with colitis. It is commonly administered on a chronic basis as an alternative to sulfasalazine therapy. The mechanism of action is unknown, but it is suspected that its activity against mycoplasmas, spirochetes, and chlamydiae is important. Best results are attained when the powdered form, labeled for use in swine, is mixed with food or added to water. Some animals may find the bitter taste unpalatable.

**Metronidazole** has fair efficacy against *Giardia*, and it is also efficacious in some cases of diarrhea in which giardiasis was not definitively diagnosed. It is suspected that this efficacy is related to the activity of metronidazole against anaerobic bacteria. Metronidazole also has an immunosuppressive effect on the GI mucosa by decreasing the cell-mediated response. Adverse neurologic effects have been reported in dogs and cats treated with metronidazole. Diazepam appears effective for treatment of neurotoxicity.

The efficacy of **glucocorticoids** for treating colitis is probably related to their anti-inflammatory and immunosuppressive capabilities. Some cases of colitis may be due to autoantibodies and T lymphocytes directed against colonic epithelial cells. Glucocorticoids suppress the immune reaction and are used when biopsy results suggest eosinophilic or plasmacytic-lymphocytic colitis. They are used in dogs, cats, and horses, often when all other forms of therapy have failed. Immunosuppressive doses of oral prednisone or dexamethasone are usually administered and slowly tapered to every-other-day therapy with the lowest effective dose.

**Budesonide** is a glucocorticoid used in people to treat asthma, rhinitis, and inflammatory bowel disease. Budesonide has a high affinity for glucocorticoid receptors, high hepatic clearance, and high local and low systemic activity compared with prednisone or dexamethasone. The human formulation of budesonide consists of coated granules with a matrix of ethyl cellulose to target release into the lumen of the ileum or ascending colon. It is not known whether the human budesonide formulation provides release in the same anatomic site in dogs, but it appears clinically effective in some dogs.

**N-3 fatty acids** have been suggested for therapy in people with ulcerative colitis or Crohn disease. The addition of n-3 fatty acids to the diet makes fewer n-6 fatty acids available for the arachidonic acid cascade. Several formulations are available for small animals, and raw linseed oil may be added to horses' grain for this effect.

Potent immunosuppressive drugs such as **azathioprine** are used to manage some forms of colitis. Azathioprine is metabolized to 6-mercaptopurine, which is immunosuppressive by interfering with nucleic acid synthesis and by impairing lymphocyte proliferation. It may take several weeks or months of therapy for azathioprine to become maximally effective. Cats particularly should be monitored for adverse effects, including myelosuppression, hepatic disease, and acute pancreatic necrosis. Chlorambucil has been used in place of azathioprine in some difficult or refractory cases of feline inflammatory bowel disease. It is too expensive to use in all but very small dogs.

## Gastrointestinal Prokinetic Drugs (Monogastric)

Prokinetic drugs increase the movement of ingested material through the GI tract. They are useful in the treatment of motility disorders, because they induce coordinated motility patterns. Unfortunately, some prokinetic drugs may produce a number of serious adverse effects that complicate their use.

The enteric nervous system of the GI tract can function independently of the CNS to control bowel function. Because there are no nerve fibers that actually penetrate the intestinal

epithelium, the enteric nervous system uses enteroendocrine cells such as the enterochromaffin cells as sensory transducers. More than 95% of the body's serotonin is located in the GI tract, and >90% of that store is in the enterochromaffin cells scattered in the enteric epithelium from the stomach to the colon. The remaining serotonin is located in the enteric nervous system, where 5-HT acts as a neurotransmitter. From the enterochromaffin cells, serotonin is secreted into the lamina propria in high concentrations, which overflow into the portal circulation and intestinal lumen. The effect of serotonin on intestinal activity is coordinated by 5-HT receptor subtypes. The 5-HT<sub>1P</sub> receptor initiates peristaltic and secretory reflexes, and so far no drugs have been developed to target this specific receptor. The 5-HT<sub>3</sub> receptor activates extrinsic sensory nerves and is responsible for the sensation of nausea and induction of vomiting from visceral hypersensitivity. Therefore, specific 5-HT<sub>3</sub> antagonists such as ondansetron and granisetron are very effective for treatment of vomiting seen with chemotherapy. Stimulation of the 5-HT<sub>4</sub> receptor increases the presynaptic release of acetylcholine and calcitonin gene-related peptide, thereby enhancing neurotransmission. This enhancement promotes propulsive peristaltic and secretory reflexes. Specific 5-HT<sub>4</sub> agonists such as cisapride enhance neurotransmission and depend on natural stimuli to evoke peristaltic and secretory reflexes. This makes these drugs very well tolerated, because they do not induce perpetual or excessive motility. It is also the reason for the limitations of these drugs, because they are not effective if enteric nerves have degenerated or become nonfunctional (as in cats with end-stage megacolon).

Table

Drug	Dosage
<a href="#">Metoclopramide</a>	Dogs and cats: 0.2–0.5 mg/kg, PO or SC, tid; 0.01–0.02 mg/kg/hr, IV infusion
	Horses: 0.125–0.25 mg/kg, diluted in 500 mL of polyionic solution and administered IV over 60 min
Domperidone	0.1–0.5 mg/kg, IM; 0.5–1 mg/kg, PO
<a href="#">Cisapride</a>	Dogs: 0.1 mg/kg, PO, tid
	Cats: 2.5 mg/cat, tid for cats <5 kg, and 5 mg/cat for cats >5 kg
<a href="#">Erythromycin</a>	0.5–1 mg/kg, PO, bid-tid
<a href="#">Ranitidine</a>	1–2 mg/kg, PO, bid
Nitazidine	2.5–5 mg/kg, PO, bid
<a href="#">Lidocaine</a>	Horses: 1.3 mg/kg, IV, as a bolus followed by a constant-rate infusion of 0.05 mg/kg/min

## Prokinetic Drugs

**Metoclopramide** is a central dopaminergic antagonist and peripheral 5-HT<sub>3</sub> receptor antagonist and 5-HT<sub>4</sub> receptor agonist with GI and CNS effects. In the upper GI tract, metoclopramide increases both acetylcholine release from neurons and cholinergic receptor sensitivity to acetylcholine. Metoclopramide stimulates and coordinates esophageal, gastric, pyloric, and duodenal motor activity. It increases lower esophageal sphincter tone and stimulates gastric contractions, while relaxing the pylorus and duodenum. Inadequate cholinergic activity is incriminated in many GI motility disorders; therefore, metoclopramide should be most effective in diseases in which normal motility is diminished or impaired.

Metoclopramide speeds gastric emptying of liquids but may slow the emptying of solids. It is effective in treating postoperative ileus in dogs, which is characterized by decreased GI myoelectric activity and motility. Metoclopramide has little or no effect on colonic motility.

Metoclopramide is primarily indicated for relief of vomiting associated with chemotherapy in dogs, as an antiemetic for dogs with parvoviral enteritis, and for treatment of gastroesophageal reflux and postoperative ileus. GI obstruction, such as intussusception in puppies with parvoviral enteritis, must be excluded before initiating metoclopramide therapy. Its prokinetic action is negated by narcotic analgesics and anticholinergic drugs, such as atropine. Drugs that dissolve or are absorbed in the stomach, such as digoxin, may have reduced absorption. Bioavailability may be increased for drugs absorbed in the small intestine. Because of accelerated food absorption, metoclopramide therapy may increase the insulin dose required in animals with diabetes.

Metoclopramide readily crosses the blood-brain barrier, where dopamine antagonism at the CRTZ produces an antiemetic effect. However, dopamine antagonism in the striatum causes adverse effects known collectively as extrapyramidal signs, which include involuntary muscle spasms, motor restlessness, and inappropriate aggression. Concurrent use of phenothiazine and butyrophenone tranquilizers should be avoided, because they also have central antidopaminergic activity, which increases the potential for extrapyramidal reactions. If recognized in time, the extrapyramidal signs can be reversed by restoring an appropriate dopamine:acetylcholine balance with the anticholinergic action of an antihistamine, such as diphenhydramine hydrochloride given IV at a dosage of 1 mg/kg.

**Cisapride** is chemically related to metoclopramide, but unlike metoclopramide, it does not cross the blood-brain barrier or have antidopaminergic effects. Therefore, it does not have antiemetic action or cause extrapyramidal effects (extreme CNS stimulation). Cisapride is a serotonin 5-HT<sub>4</sub> agonist with some 5-HT<sub>3</sub> antagonist activity, so it enhances the release of acetylcholine from postganglionic nerve endings of the myenteric plexus and antagonizes the inhibitory action of serotonin (5-HT<sub>3</sub>) on the myenteric plexus, resulting in increased GI motility and increased heart rate. Cisapride is more potent and has broader prokinetic activity than metoclopramide, increasing the motility of the colon, as well as that of the esophagus, stomach, and small intestine. Cisapride is especially useful in animals that experience neurologic effects from metoclopramide. Cisapride is very useful in managing gastric stasis, idiopathic constipation, and postoperative ileus in dogs and cats. Cisapride may be especially useful in managing chronic constipation in cats with megacolon; in many cases, it alleviates or delays the need for subtotal colectomy. Cisapride is also useful in managing cats with hairball problems and in dogs with idiopathic megaesophagus that continue to regurgitate frequently despite a carefully managed, elevated feeding program. In comparative studies of GI motility in people and animals, cisapride is clearly superior to other treatments.

Initially, the only adverse effects reported in people were increased defecation, headache, abdominal pain, and cramping and flatulence; cisapride appeared to be well tolerated in animals. As cisapride became widely used in management of gastroesophageal reflux in people, cases of heart rhythm disorders and deaths were reported to the FDA. These cardiac problems in people were highly associated with concurrent drug therapy or specific underlying conditions. In veterinary medicine, adverse reactions to clinical use of cisapride have not been reported. Cisapride for animals can only be obtained through compounding veterinary pharmacies.



**Domperidone** is a peripheral dopamine receptor antagonist that has been marketed outside the USA since 1978. It is available in Canada as a 10-mg tablet. Currently, it is available in the USA only as an investigational new drug (1% oral domperidone gel) to treat agalactia in mares due to fescue toxicosis. Domperidone regulates the motility of gastric and small-intestinal smooth muscle and has some effect on esophageal motility. It appears to have very little physiologic effect in the colon. It has antiemetic activity from dopaminergic blockade in the CRTZ. But because very little domperidone crosses the blood-brain barrier, reports of extrapyramidal reactions are rare; however, if a reaction occurs, the treatment is the same as for reactions to metoclopramide. Domperidone failed to enhance gastric emptying in healthy dogs in one study. In other studies, however, domperidone was superior to metoclopramide in stimulating antral contractions in dogs but not cats, and it improved antroduodenal coordination in dogs. Because of its favorable safety profile, domperidone appears to be an attractive alternative to metoclopramide.

**Macrolide antibiotics**, including erythromycin and clarithromycin, are motilin receptor agonists. They also appear to stimulate cholinergic and noncholinergic neuronal pathways to stimulate motility. At microbially ineffective doses, some macrolide antibiotics stimulate migrating motility complexes and antegrade peristalsis in the proximal GI tract. Erythromycin has been effective in the treatment of gastroparesis in human patients in whom metoclopramide or domperidone was ineffective. Erythromycin increases the gastric emptying rate in healthy dogs, but large food chunks may enter the small intestine and be inadequately digested. Erythromycin induces contractions from the stomach to the terminal ileum and proximal colon, but the colon contractions do not appear to result in propulsive motility. Therefore, erythromycin is unlikely to benefit patients with colonic motility disorders.

Human pharmacokinetic studies indicate that erythromycin suspension is the ideal dosage form for administration of erythromycin as a prokinetic agent. Other macrolide antibiotics have prokinetic activity with fewer adverse effects than erythromycin and may be suitable for use in small animals. Both erythromycin and clarithromycin are metabolized by the hepatic cytochrome P450 enzyme system and inhibit the hepatic metabolism of other drugs, including theophylline, cyclosporine, and cisapride. Nonantibiotic derivatives of erythromycin are being developed as prokinetic agents.

**Ranitidine** and **nizatidine** are histamine H<sub>2</sub>-receptor antagonists that are prokinetics in addition to inhibiting gastric acid secretion in dogs and rats. Their prokinetic activity is due to acetylcholinesterase inhibition, with the greatest activity in the proximal GI tract. Cimetidine and famotidine are not acetylcholinesterase inhibitors and do not have prokinetic effects. Ranitidine and nizatidine stimulate GI motility by increasing the amount of acetylcholinesterase available to bind smooth muscle muscarinic cholinergic receptors. They also stimulate colonic smooth muscle contraction in cats through a cholinergic mechanism.

Ranitidine causes less interference with cytochrome P450 metabolism of other drugs than does cimetidine, and nizatidine does not affect hepatic microsomal enzyme activity, so both drugs have a wide margin of safety.

**IV lidocaine** is used in the treatment of postoperative ileus in people and has been shown to be useful in treating ileus and proximal duodenitis-jejunitis in horses. It is thought to suppress firing of primary afferent neurons, as well as to have anti-inflammatory properties and direct stimulatory effects on smooth muscle. It is also thought to suppress the primary afferent neurons

from firing, as well as have anti-inflammatory properties and direct stimulatory effects on smooth muscle. Most horses respond within 12 hr of starting an infusion.

## Cathartic and Laxative Drugs (Monogastric)

Cathartics and laxatives increase the motility of the intestine or increase the bulk of feces. The dosages for all of these drugs are highly empirical and usually extracted from human dosages. Clinically, these drugs are administered to increase passage of gut contents associated with intestinal impaction, to cleanse the bowel before radiography or endoscopy, to eliminate toxins from the GI tract, and to soften feces after intestinal or anal surgery.

Table

Drug	Dosage
Castor oil	Dogs: 5–25 mL, PO
	Foals: 25–50 mL, PO
<a href="#">Bisacodyl</a>	Dogs: 5–20 mg, PO, once to twice daily
	Cats: 2.5–5 mg, PO, once to twice daily
<a href="#">Magnesium sulfate</a> (Epsom salts)	Dogs: 5–25 g, PO
	Cats: 2–5 g, PO
	Horses: 30–100 g, PO
Magnesium hydroxide (milk of magnesia)	Dogs: 5–10 mL, PO
	Cats: 2–6 mL, PO
	Horses: 1–4 L, PO
<a href="#">Lactulose</a>	Dogs: 5–15 mL, PO, tid
	Cats: 2–3 mL, PO, tid
Docusate sodium, docusate calcium, docusate potassium	Dogs and cats: 2 mg/kg/day, PO
	Horses: 10–20 mg/kg in 2 L water

### Cathartic and Laxative Drugs

#### Stimulant Cathartics:

Stimulant (irritant) cathartics appear to stimulate intestinal motility via an irritant effect on the mucosa or stimulation of intramural nerve plexi. They also activate secretory mechanisms, provoking fluid accumulation in the GI lumen. These drugs can have potent effects, and excessive fluid and electrolyte loss can result. They act directly or indirectly (if a metabolic conversion is necessary before the compound is active).

**Emodin** is an irritant glycoside that is an active ingredient in several products. Its action is limited to the large intestine, and it may take 4–6 hr for an effect to be seen. Repeat doses should be avoided in horses because of the long latent period and risk of severe

superpurgation. The naturally occurring emodins (eg, senna) are found in human formulations.

**Vegetable oils** are indirect-acting cathartics. They are hydrolyzed by pancreatic lipase in the small intestine to irritating fatty acids. Castor oil is a potent cathartic. It is hydrolyzed to release ricinoleic acid, which causes increased water secretion in the small intestine. Raw linseed oil (cooked linseed oil is toxic) is hydrolyzed to release linoleates, which are less irritating than ricinoleic acid. In smaller daily doses, linseed oil is a mild lubricant laxative and a source of fatty acids for horses.

**Senna** and **bisacodyl** are stimulant cathartics that affect the large intestine and are found in many over-the-counter human laxative formulations.

### Hyperosmotic Cathartics:

These drugs are poorly absorbed from the GI tract and draw fluid into the intestine by osmosis. The fluid content of the feces increases, which causes intestinal distention and promotes peristalsis. Although hyperosmotic cathartics are relatively safe, overdoses can cause excessive fluid loss and dehydration, so adequate water intake must be assured. Examples of hyperosmotic cathartics include magnesium salts, sodium salts, and sugar alcohols.

**Magnesium salts** are frequently used PO as saline purgatives. Normally, only 20% of the magnesium is systemically absorbed and eliminated by the kidneys. If absorption is excessive or renal elimination is impaired, then severe hypermagnesemia and metabolic alkalosis may develop.

**Sodium salts** can be given PO as saline cathartics but are more commonly administered as sodium biphosphate or sodium phosphate enemas. These should not be used in cats because fatal hyperphosphatemia, hypocalcemia, and hypernatremia may result.

**Sugar alcohols**, such as mannitol and sorbitol, are poorly absorbed and fermented in the terminal ileum and large intestine. Lactulose is a synthetic disaccharide fermented in the large intestine to produce acetic, lactic, and other organic acids that have an osmotic effect. Lactulose is used to treat chronic constipation in cats with megacolon. It is also used in the management of hepatic encephalopathy, in which acidification of the large intestine promotes formation of nonabsorbable ammonium ions and quaternary amines, thereby reducing the need for detoxification by the liver.

**Polyethylene glycol (PEG3350)** is a large molecular weight, water-soluble polymer used widely in people as a bulking and softening agent for treatment of constipation. It is not metabolized by the intestinal bacterial flora and is minimally absorbed by the intestines. It forms hydrogen bonds with 100 molecules of water per molecule, creating high osmotic pressures within the bowel lumen. The osmotic pressure prevents absorption of water out of the lumen. It is relatively free of adverse effects. PEG3350 is readily available in a powder form, which can be added to a dog or cat's regular food. It can also be administered as a solution via nasogastric tube. Unlike fiber laxatives, it does not cause bloating or gas.

## Hydrophilic Colloids ("Bulk Laxatives"):

The bulk laxatives use fiber to draw water in to the bowel. Fiber is made up of several different compounds, all of which are carbohydrates. The term "fiber" is used to describe the "insoluble carbohydrates" that resist enzymatic digestion in the small intestine. Found in the cell walls of plants and grains, the most common fibers are cellulose, hemicellulose, pectin, gums, and resistant starches. Almost all carbohydrate sources contain some fiber. Some of the most common sources of fiber in pet foods include rice hulls, corn and corn byproducts, soybean hulls, beet pulp, bran, peanut hulls, and pectin. Adding fiber to a diet improves colon health, helps with weight management, and helps with diarrhea, constipation, and diabetes mellitus. Many commercial brands of pet food are available in a high-fiber formula. Bulk laxatives may cause bloating and flatulence. Contrary to popular belief, bran mashes do not cause a laxative effect in horses. In cats with megacolon, high-fiber diets are used initially to help manage constipation when there is still some normal colonic motility. But once the colonic innervation has deteriorated, the diet may need to be switched to a low-residue diet with aggressive laxative treatment.

## Lubricant Laxatives:

These act by coating the surface of the feces with a water-immiscible film and by increasing the water content of the feces to provide a lubricant action. Lubricant laxatives usually contain mineral oil or white petroleum. Chronic use may reduce intestinal absorption of fat-soluble vitamins and cause a granulomatous enteritis. Mineral oil is very commonly used in horses and cattle, and commercial products are available to promote passage of hairballs in cats.

## Fecal Softeners (Surfactants):

Docusate sodium, docusate calcium, and docusate potassium are salts that decrease surface tension and allow water to accumulate in the feces. Docusate also increases cAMP in colonic mucosal cells, which increases ion secretion and fluid permeability. Usually considered very safe, concentrations of dioctyl sodium sulfosuccinate (DSS) ranging from 3–5 times the recommended dosage produced severe diarrhea, rapid dehydration, and death in horses. DSS should not be administered concurrently with mineral oil; soaps are formed and oil absorption is increased.

# Drugs Affecting Digestive Functions (Monogastric)

**Pancrealipase** contains the pancreatic enzymes lipase, amylase, and protease. It is derived from the pancreatic tissues of swine. These enzymes help digest and absorb fats, proteins, and carbohydrates. Pancrealipase is used to treat dogs and cats with exocrine pancreatic insufficiency. Several formulations are available, including oral capsules, tablets, and delayed-release capsules and tablets. The powdered forms can be added to food, and the dosage adjusted to maintain normal feces. Antacids may diminish the efficacy of pancrealipase, whereas H<sub>2</sub>-receptor antagonists may increase the amount of pancrealipase that reaches the duodenum.

**Ursodiol**, also known as ursodeoxycholic acid, is a naturally occurring bile acid. It suppresses hepatic synthesis and secretion of cholesterol and decreases intestinal absorption of cholesterol. Reducing cholesterol saturation allows solubilization of cholesterol-containing gallstones. Ursodiol also increases bile flow and reduces the hepatotoxic effect of bile salts by decreasing their detergent action. In small animals, ursodiol may be useful in treatment of cholesterol-containing gallstones, idiopathic hepatic lipidosis, and chronic active hepatitis. The dosage in dogs and cats is 15 mg/kg/day, PO.

**S-Adenosylmethionine (SAMe)** is an endogenous molecule synthesized by cells throughout the body. Formed from the amino acid methionine and ATP, SAMe is an essential part of three major biochemical pathways: transmethylation, transsulfuration, and aminopropylation. Deficiency of SAMe is associated with cellular derangements in hepatocytes, and there is evidence that a SAMe deficiency may contribute to abnormalities of cellular structure and function in many body tissues, including the liver. Exogenous administration of SAMe appears to improve hepatocellular function in in vivo and in vitro studies without cytotoxicity or significant adverse effects. SAMe increases hepatic glutathione levels in cats and dogs. Glutathione is a potent antioxidant that protects hepatic cells from toxins and death. The daily dosage is 18 mg/kg, rounded to the nearest size of enteric-coated tablet, and given on an empty stomach.

**Milk thistle** is used as a natural remedy for diseases of the liver and biliary tract. Silymarin is the active extract and contains flavonignans that reportedly act as antioxidants, scavenging free radicals and inhibiting lipid peroxidation. Several controlled clinical trials have demonstrated the benefits of milk thistle in human patients with acute or chronic liver disease. A veterinary formulation has been approved in the USA for dogs and cats.

## The Ruminant Digestive System

Other than the forestomachs (rumen, reticulum, omasum), the components of the ruminant GI tract are similar to those of monogastric mammals, and the use of pharmacologic agents to treat diseases of the glandular stomach (abomasum) and intestine follows principles common to both monogastric and ruminant species. Ruminants differ significantly from other mammals in that much of their feed undergoes microbial predigestion in the forestomachs, chiefly in the rumen and reticulum. There is also postgastric fermentation in the cecum and colon, but this is much less important than in some other herbivores, eg, horses.

Ruminoreticular motility or fermentation is depressed in many conditions, including improper feeding (overload or deficiency of specific nutrients), lack of water, infectious diseases, intoxications, lesions of any part of the upper GI tract, metabolic states (eg, hypocalcemia), or reduced flow of alkaline saliva that allows pH to fall and the microbial population to be altered to an extent that is harmful to the animal.

The primary objectives of pharmacotherapy are to remove the cause and to promote the return of normal digestive function by meeting or reestablishing the requirements for optimal ruminoreticular function as quickly as possible. This may include any of the following: 1) ensuring an appropriate substrate for microbial fermentation; 2) providing any cofactors (eg, phosphorus, sulfur) necessary for microbial fermentative processes; 3) removing any soluble end-products, undigested solid residues, and gas; 4) maintaining continual flow culture of ruminal microorganisms; 5) ensuring that the contents of the ruminoreticulum are fluid; 6)

maintaining optimal intraruminal pH (generally between 6 and 7); and 7) promoting active ruminoreticular activity.

## Drugs for Specific Purposes in the Ruminant Digestive System

### Esophageal Obstruction:

Esophageal obstruction due to a foreign body leads to severe discomfort and acute free-gas bloat. Physical removal of the object may be hampered by marked spasm of the surrounding muscle. Specific spasmolytic drugs such as acepromazine may be used (0.05–0.1 mg/kg, IV, IM, or SC in cattle). Alternatively, the moderate sedative and muscle relaxant effects of a low dose of xylazine (0.05 mg/kg, IM in cattle) or detomidine (0.02–0.05 mg/kg, IM in cattle) may aid removal of obstructions. None of these compounds has been approved by the FDA for use in cattle.

### Ruminotorics:

Agents and mixtures that promote forestomach function (fermentation and motility) are known as ruminotorics. Formulations that contain glucogenic substrates, minerals, cofactors, and bitters (eg, nux vomica) have limited application in current therapy of ruminoreticular indigestion. Generally, restoration of the normal ruminoreticular environment using a physiologic approach is much more satisfactory.

Oral administration of specific alkalinizing or acidifying agents should not be routinely undertaken in cases of indigestion. Magnesium oxide or magnesium hydroxide are strongly alkalinizing agents able to substantially increase rumen pH and thus create a hostile environment for rumen protozoa. These compounds, when given at label dose to dairy cattle, result in significant decrease in rumen fermentation and a decrease in number of rumen protozoa. Therefore, these compounds should only be administered to cattle with a confirmed diagnosis of grain overload.

Mineral oil (1–2 L) or dioctyl sodium sulfosuccinate (DSS, 90–120 mL in 1–2 L of water) administered PO or via nasogastric tube followed by gentle ruminal massage can help promote the dissolution and passage of impacted fibrous ruminal omasal or abomasal contents. DSS can markedly depress rumen protozoa; thus, ruminal transfaunation should follow use of this agent if ruminal hypomotility continues.

### Ruminal Fluid Transfer:

Fresh ruminal fluid is considered to be the best available “ruminotoric,” because it contains viable ruminal bacteria ( $1 \times 10^8$ – $10^{11}$ /mL) and protozoa ( $1 \times 10^5$ – $10^6$ /mL) as well as many useful fermentation factors (volatile fatty acids, microbial protein, minerals, vitamins, buffers). Strained fresh ruminal juice (at least 3 L, but 8–16 L is ideal in cattle; sheep require ~1 L) given PO or by tube is indicated in cases of ruminoreticular stasis. Ruminal fluid can be aspirated through a stomach tube from the ruminoreticulum of healthy animals using an extractor pump or by siphoning, or it can be collected at slaughterhouses. A rumen-cannulated

donor animal is particularly convenient. It is best for the donor to be on a ration similar to that of the recipient, because the ruminal microflora will then be more appropriately adapted. Provided the initiating condition or lesion is responding favorably, improvement almost invariably follows the reestablishment of normal ruminal microflora, with consequent normalization of the fermentation process and ruminoreticular motility. When the ruminoreticular contents are putrefied, ingesta must first be removed before transfer of fresh ruminal fluid. This can be accomplished using a large-bore stomach tube or by performing a rumenotomy. Acetic acid (vinegar, 4–10 L, PO) can be administered to cattle with putrefaction of the rumen associated with high rumen pH.

### **Antifoaming Agents:**

Therapeutic approaches to the control of acute frothy bloat involve administration of antifoaming agents to reduce foam stability and to promote release of free gas, which is then promptly eructated. Acute frothy bloat in cattle should be treated with poloxalene, which may be administered as a drench or by stomach tube (25–50 g). Frothy bloat can be prevented by administering poloxalene as a top dressing to feed (1 g/45 kg body wt/day) or in a molasses block (1.5 g/45 kg body wt/day). Polymerized methyl silicone (3.3% emulsion [cattle: 30–60 mL; sheep: 7–15 mL]) may be used in a similar manner as poloxalene, although direct intraruminal injection via a needle or cannula may be more satisfactory in this case. Administration of docusate sodium in emulsified soybean oil (6–12 fl oz containing 240 mg/mL) or administration of vegetable oils alone, such as peanut oil, sunflower oil, or soybean oil (cattle: 60 mL; sheep: 10–15 mL), also relieves acute frothy bloat when given PO. The incidence of frothy bloat in feedlot cattle may be reduced by including ionophores (such as monensin) either in the ration or administering as controlled-release capsules.

### **Ruminoreticular Antacids:**

Ruminal alkalinizing agents are principally used to treat ruminal lactic acidosis (pH <5.5) due to grain engorgement or soluble carbohydrate overload. The resultant systemic dehydration and acidosis necessitate immediate correction of fluid and electrolyte balance and restoration of a viable microbial population. Often, the latter involves removal of ruminoreticular contents and replacement with fresh ruminoreticular fluid. Antacids that may be given PO, bid-tid, include magnesium hydroxide (cattle: 100–300 g; sheep: 10–30 g) and magnesium carbonate (cattle: 10–80 g; sheep: 1–8 g). Antacids should be mixed in ~10 L of warm water to ensure adequate dispersion through the ruminoreticular contents. Administration PO of activated charcoal (2 g/kg) is believed to protect the ruminoreticular mucosa from further injury by inactivating toxins. Oral administration of sodium bicarbonate (baking soda), either as powder dissolved in water or commercially available solutions prepared for IV infusion, rapidly neutralize the rumen pH but are accompanied by rapid release of large amounts of CO<sub>2</sub>. Because of decreased rumen motility in ruminants with acute rumen acidosis, these animals are at increased risk of developing potentially life-threatening free gas bloat.

### **Ruminoreticular Acidifying Agents:**

Ruminal acidifying agents are used to treat ruminal stasis or simple indigestion as well as acute ammonia poisoning. In ruminal stasis, the intraruminal pH often increases to >7.5 because of the constant inflow of bicarbonate-rich saliva in the absence of active ruminal fermentation and formation of volatile fatty acids. In acute ammonia intoxication, the



increased intraruminal pH increases the activity of urease and facilitates the absorption of free ammonia ( $pK_a$  of ammonium is 9.1). Administration of weak acids in cold water returns the pH of ruminoreticular content toward physiologic levels, promotes the uptake of volatile fatty acids, depresses the absorption of ammonia, and inhibits excessive urease activity. Acetic acid (4%–5%) or vinegar (cattle: 4–8 L; sheep: 250–500 mL) is the most common acidifying agent used.

### **Modulators of Ruminoreticular Motility:**

The use of motility modifiers in cattle is controversial, because evidence-based data demonstrating clinical efficacy are scarce. Several diseases, including paralytic ileus, cecal dilatation, and abomasal displacement, are accompanied by GI tract motility disorders. Pharmacologic motility modification may hasten recovery in some cases. However, in most instances, the most effective strategy to reestablish motility is correction of the underlying disorder (hypocalcemia, endotoxemia, alkalemia, obstruction, or organ displacement) followed by restoration of the normal ruminoreticular environment through transfaunation. Furthermore, conditioned responses to the presence of feed and feeding itself are physiologic means by which ruminoreticular motility can be notably enhanced.

Motility modifiers are categorized based on their mechanism of action. These can be cholinergics (parasympathomimetics), adrenergics, antidopaminergics, serotonergics, motilin agonists, opioid receptor blockers, or sodium channel blockers (lidocaine).

The use of parasympathomimetic agents (eg, neostigmine, physostigmine, bethanechol) is seldom appropriate. These drugs have cholinergic effects, which are potentially hazardous. Neostigmine (cattle: 0.02 mg/kg, SC; sheep: 0.01–0.02 mg/kg, SC) generally produces the fewest adverse effects but tends to increase frequency, rather than strength, of ruminoreticular contractions. Neostigmine given as a constant-rate IV infusion (87.5 mg in 10 L of sodium-glucose infusion at 2 drops/sec) has been used to treat cecal dilatation/dislocation. However, the stimulatory effect of neostigmine is not always reliable, and some inhibition of motility can be seen. This may be due to the adrenergic component associated with ganglion stimulation by cholinergic agents.

Bethanechol (0.07 mg/kg, SC, tid for 2 days) has been used to treat spontaneous cecal dilatation without torsion. Potential adverse effects include salivation and diarrhea. Recommendations involving neostigmine and bethanechol have not been confirmed in randomized, controlled experiments. Neither compound has been approved by the FDA for use in cattle. Parasympathomimetics are sometimes used in practice to conservatively treat left displaced abomasum in cows, although the literature indicates that use of these compounds is of no value for this purpose.

N-butylscopolammonium bromide (nonlactating adult cattle: 0.2 mg/kg, IM or IV; calves: 0.4 mg/kg, IM or IV) is a parasympatholytic agent approved for the control of diarrhea in cattle in some European countries. The commercial formulation is combined with an NSAID, metamizole (nonlactating adult cattle: 25 mg/kg, IM or IV; calves: 50 mg/kg, IM or IV). Administration of N-butylscopolammonium bromide (80 mg/cow) in combination with dipyrone has been proposed as a conservative treatment of spontaneously occurring right-side displacement of the abomasum in cattle. However, this has not been demonstrated in randomized, controlled studies. N-butylscopolammonium bromide is not approved by the FDA, and the use of dipyrone in food animals in the USA is prohibited.

Atropine (0.04 mg/kg, IV) has been found to mitigate abomasal contractions for 1–3 hr. Atropine sulfate (0.5 mg/kg, IV) administered 5 min before placement of a reticular magnet is suggested to prevent magnet loss into the cranial sac of the rumen. Atropine (40 mg/cow as a 1% solution, SC) is also used to determine disruption of forestomach motility in cattle suspected to have vagal indigestion. An increase of >16% in heart rate 15 min after atropine administration is considered indicative of severe disruption of forestomach motility.

Xylazine hydrochloride (0.2 mg/kg, IV) administered 5 min before placement of a reticular magnet may prevent loss into the cranial sac of the rumen but will also result in deep sedation of the animal and thus is unlikely to be of any practical use. Xylazine-induced atony of the reticulorumen may be reversed by pretreatment with tolazoline (0.5 mg/kg, IV), atipamezole hydrochloride (0.08 mg/kg), or yohimbine (0.2 mg/kg, IV). Adverse effects of xylazine in cattle include bradycardia, hypothermia, salivation, diuresis, ruminal bloat, and aspiration pneumonia. Neither xylazine nor its antidotes have been approved by the FDA for use in cattle.

Metoclopramide (cattle: 0.15 mg/kg, IM; sheep: 0.023–0.045 mg/kg) has cholinergic and antidopaminergic effects but does not appear to increase the myoelectric activity of the pyloric antrum in either species. However, metoclopramide at 0.5 mg/kg given IM or IV to goats has been shown to increase myoelectric activity of the pyloric antrum but not the body of the abomasum. Because metoclopramide can cross the blood-brain barrier, restlessness and excitement are potential adverse effects. Metoclopramide has not been approved by the FDA for use in cattle.

Erythromycin lactobionate is a macrolide antimicrobial that increases gut myoelectric activity by binding to motilin receptors in intestinal smooth muscle cells. In cows, erythromycin (0.1 mg/kg, IV, or 1 mg/kg, IM) was found to increase myoelectrical activity in the abomasum and duodenum for >2 hr. This effect was increased to 6–8 hr when erythromycin was administered in polyethylene glycol at 10 mg/kg, IM. Erythromycin is approved by the FDA only for treatment of shipping fever, pneumonia, footrot, and metritis at 2.2 mg/kg, IM. Deep IM injection in muscles of the neck is recommended because of the risk of pain, swelling, and tissue blemishes at the injection site.

The prokinetic serotonergic drug cisapride (cattle: 0.08 mg/kg) is widely used in equine medicine, yet significant prokinetic effects have not been conclusively demonstrated in ruminants. Furthermore, definitive clinical and experimental data to support the use of opioids or lidocaine in ruminants have not been published.

## Drug Disposition in the Ruminoreticulum

Morphologic and functional characteristics of the ruminoreticulum that make it suitable for fermentative digestion of plant material also affect the activity, distribution, and absorption of many drugs, particularly when given PO. The anaerobic and reductive environment of the

ruminoreticulum and the presence of many microbial enzymes result in inactivation of drugs such as trimethoprim and cardiac glycosides. Slow and inefficient mixing of drugs in the large volume of the ruminoreticular fluid delays attainment of uniform concentrations throughout the multiphasic ingesta and retards absorption from the ruminoreticulum. Absorption is also affected by the polarity and ionization status of the drug, which is determined by the  $pK_a$  of the drug and the pH of the ruminoreticular fluid. The latter depends on the diet and the relative contributions of alkaline saliva and acidic ruminoreticular fluid. Aside from the many effects that the ruminoreticular environment can have on the activity and disposition of drugs, the drugs themselves may have unintended effects on ruminoreticular function. In particular, broad-spectrum antibacterial agents and antiprotozoal agents can disrupt the normal balance of microflora in the ruminoreticulum.

These factors affecting the activity and disposition of drugs in the ruminoreticulum, together with the possible effects of drugs on ruminoreticular function, complicate oral administration of drugs to ruminants. In young animals, these undesirable effects can be avoided by making use of the esophageal groove reflex. This reflex, which is elicited by receptors in the mouth and pharynx, is well developed in suckling neonates but becomes less reliable in older animals. After ~24 mo in cattle and ~18 mo in sheep, provoked reticular groove closure is often irregular, incomplete, or absent.

Ruminoreticular morphology and function has less influence on drug disposition in neonatal ruminants than in adults. At birth, the forestomachs are underdeveloped, and the newborn ruminant is essentially monogastric. Drugs that are usually destroyed in the ruminoreticulum of adults (eg, trimethoprim) may be well absorbed during the first 2–3 wk of life. This developmental pattern depends on the period between birth and initiation of a roughage diet and exposure to microbes in the environment.