central noradrenergic and serotonergic activity. In animals it has appetite-stimulating and antinausea properties. These effects are attributed to the 5-HT_3 antagonist properties; therefore, it may share similar effects as antiserotonin medications discussed in Section Serotonin Antagonists.

Clinical Use

Mirtazapine has been studied more in cats than in dogs (Quimby and Lunn, 2013). These studies in cats demonstrated that it is an effective appetite stimulant. The dose is usually 1.88 mg per cat oral. At high doses it produces adverse effects that include vocalization and increased restlessness. In cats it has a half-life of approximately 10 hours, which allows for once-daily dosing. In cats with chronic kidney disease – for which appetite stimulation often is desired – clearance is slower and the half-life increases to 15 hours, which indicates that an every-other-day dosing schedule should be used in cats with kidney disease to avoid accumulation (Quimby et al., 2011). Mirtazapine is available as 7.5-mg tablets, but also is available in 15, 30, and 45-mg sizes. The formulation that some veterinarians prefer is a rapidly disintegrating oral tablet that dissolves easily in an animal's mouth (15, 30, and 45 mg).

Gastrointestinal Prokinetic Drugs

Prokinetic drugs increase gastrointestinal motility (Washabau and Hall, 1997). They are used in dogs, cats, horses, and occasionally ruminants to stimulate gastric emptying, rumen motility, or to increase intestinal motility (Whitehead et al., 2016). Intestinal motility is sometimes decreased after intestinal disease or surgery and can lead to ileus. Some of these drugs are intended to restore normal motility to facilitate recovery.

Metoclopramide (Reglan®, Maxeran®)

Metoclopramide has multiple actions. It is a dopamine (DA_2) antagonist, serotonin (5-HT_4) agonist and serotonin (5-HT_3) antagonist. Among the proposed mechanisms of metoclopramide is an increase in the release of acetylcholine in the GI tract, possibly via a prejunctional mechanism. It also may increase motility of gastric smooth muscle by increasing sensitivity of the cholinergic response. Since it also is a dopamine antagonist, it may antagonize dopamine's (DA_2) inhibitory action on GI motility.

Metoclopramide increases gastric emptying, increases the tone of the esophageal sphincter, and stimulates motility of the duodenum. It has less effect on distal segments of the intestine. Metoclopramide acts centrally to inhibit DA_2, which produces the antiemetic effects discussed in Section Antiemetic Drugs. In people, metoclopramide also has been used to treat hiccups and lactation deficiency.

Adverse effects from metoclopramide can include excitement (seen in horses, for example), anxiety, and involuntary muscle movements. There are also endocrine effects: There is a transient increase in prolactin and aldosterone. *Since some breast cancers are prolactin-dependent, there has been some concern about the carcinogenicity of this drug in women.*

Use in Small Animals

In dogs metoclopramide has been used as an antiemetic more commonly than other drugs. Although it has been used to promote GI motility as well, this effect is less established than previously thought (Whitehead et al., 2016). For example, it is of little benefit to increase stomach emptying in disorders of gastroparesis or chronic regurgitation. It also has been used to stimulate normal upper motility following surgery (e.g., corrective surgery for gastric dilatation), but one study showed that metoclopramide did *not* change gastric motor activity to promote gastric emptying in dogs with gastric dilatation volvulus (Hall et al., 1996). In another study, it reduced, but did not prevent gastroesophageal reflux in anesthetized dogs at a dose of 1 mg/kg (Wilson et al., 2006). Doses are in the range of 0.25 to 0.5 mg/kg, q 8–12 h, but they have been increased to 1–2 mg/kg.

Use in Horses

Some equine surgeons have used infusions of metoclopramide (0.125–0.25 mg/kg/h) added to IV fluids to reduce postoperative ileus in horses (Gerring and Hunt, 1986). It may stimulate small intestine – but not large bowel – motility, but this has little benefit for horses with intestinal ileus (Sojka et al., 1988). Undesirable side effects in horses have been common, and include behavioral changes and abdominal pain. Since this drug transiently increases prolactin secretion, there has been interest in using this drug for treating agalactia in animals, but efficacy has not been determined. Domperidone is preferred for this effect (see Section Domperidone (Motilium, Equidone)).

Use in Ruminants

The clinical use of metoclopramide in large animals has not been as common as in small animals. Metoclopramide has little usefulness in cattle, although it may increase the motility of the rumen in cattle and sheep. It has been used successfully in some cattle with functional pyloric stenosis (Braun et al., 1990), but was not effective in calves (0.1 mg/kg IM). At doses higher than 0.1 mg/kg in calves it caused severe neurological side effects (Wittek and Constable, 2005).

Domperidone (Motilium, Equidone)

Domperidone is a dopamine-2 receptor (DA_2) antagonist. It may also have α_1-receptor antagonist and serotonin (5-HT_2) antagonist effects. It has been available as a 10-mg tablet outside the USA as a human prokinetic drug but not allowed for human use in the USA because of cardiac toxicity. Its mechanism of action and GI prokinetic effects are similar to metoclopramide, but its efficacy has not been very impressive in animals and thus a clinical use has not been recommended (Whitehead et al., 2016). A difference between metoclopramide and domperidone is that the latter does not cross the blood–brain barrier. Therefore, adverse CNS effects are not as much of a problem compared to metoclopramide in horses. It may have antiemetic properties, but only if the stimulus for vomiting affects the CRTZ. It is capable of reaching the area postrema of the brain because this area is not protected by the blood–brain barrier. An additional effect is to stimulate lactation (see Section Use in Horses).

Use in Small Animals

The use is not reported, but it will produce a prokinetic effect in dogs at a dose of 0.05–0.1 mg/kg (2–5 mg/animal).

Use in Horses

Domperidone has been investigated for use in horses to treat fescue toxicity and agalactia. Fescue toxicosis is caused by a fungus that produces a toxin that induces reproductive toxicity in horses. The action of domperidone to increase lactation is through the stimulation of prolactin. It is approved by the FDA as an equine formulation of domperidone (Equidone oral gel, 11%). The approved dose is 1.1 mg/kg once daily starting 10–15 days prior to the anticipated foaling date. Treatment may be continued for up to 5 days after foaling if mares are not producing adequate milk. (This dose is equivalent to 5 ml per 500 kg – 5 ml per horse – daily, PO of the 11% oral gel.) Do not administer with stomach antacids such as omeprazole, cimetidine, or antacids.

The prokinetic effects in horses are not very impressive. At an IV dose of 0.2 mg/kg it was effective at restoring motility in horses with ileus, but this drug is not available in an injectable formulation. The oral absorption in horses is only 1.2–1.5%. Oral administration of 1.1 mg/kg (the approved dose) had no effect on GI function in horses but at 5 mg/kg it increased stomach emptying (Nieto et al., 2013).

Another use of domperidone is to increase digital laminar microvascular blood flow in horses. This effect is presumed to be via the action as an antagonist on vascular α_2-adrenergic receptors. It was shown to increase laminar microvascular blood flow in normal horses (1.1 and 5.5 mg/kg oral), but has not been evaluated clinically for treatment of laminitis (Castro et al., 2010).

Cisapride

In July 2000, cisapride (formerly called Propulsid®) was removed from the market because of serious cardiac adverse events, and some deaths in people, secondary to cardiac arrhythmias. The drug sponsor has no plans to market this drug to veterinarians, but there is continued interest among veterinarians and it is still available via compounding pharmacists. Until other new replacement drugs become available, such as prucalopride or mosapride, veterinarians will rely on compounded formulations or consider alternative drugs.

The reviews on cisapride by Washabau and Hall (1995) and Van Nueten and Schuurkes (1992) describe the details of its mechanism of action and clinical effects. Cisapride has greater prokinetic effects in comparison to the other drugs discussed thus far. Its mechanism is believed to be as an *agonist* for the 5-hydroxytryptamine (5-HT_4) receptor on myenteric neurons (5-HT_4 ordinarily stimulates cholinergic transmission in the myenteric neurons). (Serotonin and antagonists/agonists are covered in more detail in Chapter 19.) Cisapride may also be an *antagonist* for the 5-HT_3 receptor. Via these mechanisms – or independently – cisapride may enhance release of acetylcholine at the myenteric plexus. There is evidence that, in cats, cisapride directly stimulates smooth muscle motility via an unknown noncholinergic mechanism (Washabau and Summarco, 1996). Cisapride increases the motility of the stomach, increases stomach emptying, and increases motility of the small intestine and colon. It accelerates the transit of contents in the bowel and intestines. Because of the 5-HT_3 antagonist properties, it also has some antiemetic effects. Other drugs with a similar mechanism of action have been investigated, but are not in clinical use. One such drug is mosapride. Like cisapride, mosapride is also a 5-HT_4 agonist and has been approved in some countries for treating upper gastrointestinal motility disorders in dogs (Chae et al., 2015). It has been studied in experimental horses and demonstrated to increase motility of the small intestine and cecum at a dose of 1.5–2 mg/kg PO (Sasaki et al., 2005).

Pharmacokinetics

Oral absorption is variable because of extensive metabolism. The oral absorption in dogs and cats ranges from 30 to 60%. In horses, rectal absorption has been attempted, but the amount absorbed systemically is negligible (Cook et al., 1997).

Elimination half-life is variable, but ranges from an average of approximately 5 hours in dogs and cats to a much faster rate in large animals, 2 hours or less in horses and ruminants. The volume of distribution is high

in small animals (>4 l/kg) and approximately 1.5 l/kg in large animals.

Use in Dogs

In dogs at a dose of 0.1 mg/kg (range 0.08–1.25 mg/kg) orally, it stimulates smooth muscle of the stomach, small intestine, and colon, with a duration of effect of about 3 hours. Routine clinical doses have ranged from 0.1 to 0.5 mg/kg every 8–12 hours.

Although cisapride has been used by some veterinarians for treatment of megaesophagus in dogs, the response is usually poor. The canine esophagus is striated muscle, with no smooth muscle to directly respond to the medication. Clinical use in dogs has included treatment for gastroesophageal reflux, delayed gastric emptying, and small bowel motility disorders. Compared to metoclopramide, cisapride is more effective for increasing lower esophageal sphincter tone in dogs, which is helpful for preventing reflux esophagitis (Kempf et al., 2014).

Use in Cats

Experiments have demonstrated that cisapride causes stimulation of the entire GI tract in cats. Of particular interest is the effect of cisapride on colonic smooth muscle. Cisapride will stimulate this motility and has been used for treating chronic constipation. By contrast, metoclopramide has no effect on colonic smooth muscle. The dose of cisapride in cats is approximately 2.5 mg per cat, two or three times daily. Doses as high as 1 mg/kg every 8 hours, or 1.5 mg/kg every 12 hours have been recommended by some investigators (LeGrange et al., 1997).

Use in Horses

In horses cisapride increases the motility of the left dorsal colon and improves ileocecocolonic junction coordination. In contrast to metoclopramide, cisapride has fewer side effects at doses needed to affect the GI tract and greater effects on the jejunum and colon than metoclopramide. Many investigators believe that it has a place in the postoperative management of horses that have undergone abdominal surgery. One dose tested to be effective was 0.1 mg/kg, IV. At this dose, the effects appear to persist for approximately 2 hours. Oral administration is usually not possible in these horses because of gastric reflux and absorption after oral administration in a horse with gastric reflux probably is questionable.

Availability of Formulations

The previously available tablet was a 10-mg tablet from Janssen Pharmaceutica. Although cisapride is insoluble in most aqueous solutions, solubility is possible in acidic solutions. An IV form may be created by preparing a 4 mg/ml solution in tartaric acid by a reputable compounding pharmacist. The preparation of this formulation was described in the publication by Cook et al. (1997). To prepare this solution, 40 mg of cisapride is combined with 1 ml of 0.4 M tartaric acid. After the cisapride is dissolved, dilute with water to obtain a total volume of 10 ml. Oral formulations for cats have been prepared from the bulk powder administered in a capsule, via a suspension in a flavored vehicle or dissolved in cod liver oil.

Side Effects and Interactions

Adverse effects have not been reported in animals; however, abdominal discomfort has been observed when animals received high doses. In safety studies, dogs have tolerated high doses (40 mg/kg) for prolonged periods without problems.

In people, high plasma concentrations have caused cardiac arrhythmias. The arrhythmias are caused by prolonged QT intervals, presumably from blockade of potassium channels. This can lead to serious arrhythmias and has been responsible for deaths in people. These reactions have not been reported for animals. Nevertheless, one should be cautious about combining cisapride with drugs such as itraconazole and ketoconazole that may increase plasma concentrations by interfering with metabolism.

Bethanechol (Urecholine)

Many of the formulations of bethanechol have been discontinued and are no longer marketed. Some generic forms may still remain and veterinarians have also obtained it through compounding pharmacies. This drug is a cholinergic agonist that has been used to nonspecifically stimulate smooth muscle. It binds to muscarinic receptors and initiates GI smooth muscle contractions, but its actions are nonspecific. In contrast to cisapride or metoclopramide, bethanechol has a more pronounced effect on motility of the ileocecocolic region in cattle (0.7 mg/kg). In horses, bethanechol increases gastric emptying at a dose of 0.025 mg/kg IV (Ringger et al., 1996). One of its other uses has been to stimulate contraction of bladder smooth muscle in animals that have a failure to completely empty their urinary bladder when voiding. Adverse effects are common and include diarrhea and other consequences of cholinergic stimulation.

Neostigmine (Prostigmin)

Neostigmine inactivates the enzyme acetylcholinesterase, which results in inhibition of degradation of acetylcholine at the synapse. It prolongs the action of acetylcholine and may directly stimulate cholinergic

receptors. It is short acting. In horses, its use is discouraged because it may actually decrease intestinal propulsive contractions, delay gastric emptying, and cause abdominal discomfort.

One of the other uses of neostigmine in animals is for the treatment of neuromuscular diseases such as myasthenia gravis. Its adverse effects are significant, and include diarrhea, salivation, respiratory difficulty, vomiting, and muscle twitching. (Usually, another anticholinesterase drug, pyridostigmine, is preferred for treating myasthenia gravis because it has fewer side effects.)

H_2-Receptor Antagonists

H_2-receptor blockers such as ranitidine and nizatidine have prokinetic effects on intestinal smooth muscle in animals. These drugs are discussed later in Section Drugs for Treatment of Gastrointestinal Ulcers in Animals.

Erythromycin

Erythromycin is a macrolide antibiotic ordinarily used to treat bacterial infections. Pharmacology of macrolides is discussed in Chapter 36. It has long been associated with vomiting and regurgitation in small animals as an adverse consequence of treatment. This effect is caused by stomach contraction and expulsion at high doses. However, at low doses it can produce a beneficial stimulation of GI motility. Not all macrolide antibiotics exhibit this property because it requires a unique chemical structure that not all drugs in this class possess. (Erythromycin has a 14 carbon structure, but other macrolides that are less effective – tylosin and tilmicosin – have a 16 carbon structure.)

Erythromycin stimulates GI motility via activation of motilin receptors, via release of endogenous motilin, or via cholinergic mechanisms in the upper GI tract (Hall and Washabau, 1997; Lester et al., 1998; Hawkyard and Koerner, 2007). Motilin is a 22 amino acid peptide released from endocrine cells of duodenal mucosa. It increases the motor contractions, the housekeeper wave, during the interdigestive period. Motility is stimulated specifically in the pyloric antrum or the smooth muscle cells of the proximal small intestine (Nouri and Constable, 2007; Nouri et al., 2008). Because most of the motilin receptors are on the stomach and proximal small intestine, there is a weak response to erythromycin in the distal GI tract. In people, erythromycin has been used to promote gastric motility and increase stomach emptying in patients with diabetic gastroparesis and used in conjunction with enteral feeding in critical care patients (Hawkyard and Koerner, 2007).

The effective dose is 1 mg/kg or less – much lower than the antibacterial dose. It was effective for stimulating motility in experimental horses (Ringger et al., 1996), but clinical responses to erythromycin in horses have been somewhat disappointing. One study showed that responses to erythromycin in horses that had undergone surgery were not as effective as the effects in healthy horses (Roussel et al., 2000). A dose of 8.8 mg/kg IM increased abomasal and rumen motility in calves (Nouri and Constable, 2007; Nouri et al., 2008; Wittek and Constable, 2005). The dose in small animals is also in the range of 0.5–1 mg/kg, but has not been tested for clinical efficacy (Whitehead et al., 2016). There is a concern that erythromycin may cause diarrhea in some horses through the effect on the normal bacterial flora of the intestine. An additional concern is that routine use may promote antibacterial resistance.

Lidocaine

Lidocaine is a well-known local anesthetic. (Local anesthetics are covered in more detail in Chapter 15, and with antiarrhythmics in Chapter 22.) It is used for local infiltration for minor surgical procedures and to treat cardiac arrhythmias. Intravenous infusions of lidocaine also improve intestinal motility in horses. Lidocaine has been used in horses postsurgically to reduce postoperative ileus. Postoperative ileus in horses is a widespread clinical problem that may be caused by (i) sympathetic stimulation, (ii) pain, or (iii) inflammation. These effects inhibit smooth muscle motility in the intestine and lidocaine may work by suppressing this transmission. Another view on the mechanism is that lidocaine does not have a direct prokinetic effect, but rather restores motility via other mechanisms (Cook and Bilkslager, 2008). These authors presented evidence that in horses lidocaine restores motility by inhibiting intestinal inflammation and reperfusion injury.

In one study (Malone et al., 2006), lidocaine administration to horses produced less reflux and shorter time of hospitalization. Infusions of lidocaine have decreased postoperative ileus either through a direct effect, or via suppression of painful stimuli. Doses in horses are 1.3 mg/kg loading dose (bolus), followed by 0.05 mg/kg/min IV infusion.

Adverse Effects

As with the other uses of lidocaine, systemic administration may produce adverse events. The most common in horses have been muscle fasciculations, ataxia, and seizures. If signs are observed, decrease rate of infusion.

Opiate Antagonists for Promoting Intestinal Motility

Opiates and their antagonists are discussed in Chapter 13. Activation of opiate μ receptors in the intestinal

smooth muscle decreases propulsive motility. Expression of μ-opiate receptors have been found in the submucosal plexus, myenteric plexus, and longitudinal muscle of the ileum. Activating these receptors has been used to treat some forms of diarrhea (e.g., loperamide). Administration of opiate analgesics postoperatively (Boscan et al., 2006; Sojka et al., 1988) or increased levels of endogenous opioids (endorphins), stimulate these receptors to inhibit intestinal motility causing postoperative ileus (DeHaven-Hudkins et al., 2008). Therefore, postoperative ileus may be treated by blocking intestinal opiate receptors (μ receptors) (Hicks et al., 2004).

Selective peripheral opiate antagonists act as peripheral opioid antagonists, rather than central opioid antagonists. They do not produce a central effect because they are unable to cross the blood–brain barrier. *Naloxone should not be used for this indication because it will cross the blood–brain barrier to diminish the analgesic effect of opioids.* Such agents include alvimopan, methylnaltrexone, and naloxegol.

Alvimopan (Entereg®) has advantages over methylnaltrexone with respect to potency and duration of activity (DeHaven-Hudkins et al., 2008; Taguchi et al., 2001). It is administered orally with low bioavailability (6%) and produces a local effect on the intestine to promote motility, without diminishing analgesic effect of opioids. It is a zwitterionic molecule and the high polarity restricts its diffusion across the blood–brain barrier. A dose of 3 mg orally to people, three times daily completely reversed the GI effects of morphine, without affecting analgesia. The typical dose is 12 mg (one capsule) administered orally prior to surgery, and continuing after surgery twice daily.

Methylnaltrexone (Relistor®) is available as a SC injection (0.15 mg/kg) administered once every 48 hours for postoperative ileus. Like alvimopan, it does not have systemic effects and will not interfere with analgesia. There has been limited use of methylnaltrexone in horses. At a dose of 0.75 mg/kg IV q 12 h for four days to horses inhibited morphine-induced intestinal effects (Boscan et al., 2006).

Naloxegol (Movantik®), in 12.5 and 25-mg tablets, is a pegylated opioid antagonist. It is used for oral treatment of opioid-induced constipation. It acts peripherally because pegylation of the molecule reduces the ability of naloxegol to cross the blood–brain barrier and makes it a substrate for the efflux transporter P-glycoprotein.

Drugs for Treatment of Gastrointestinal Ulcers in Animals

Histamine H_2-receptor antagonists, sucralfate, proton pump inhibitors (omeprazole), and antacids remain the principal drugs used to manage gastrointestinal ulceration in small and large animals (Table 46.3; Figure 46.1). The medical management of ulcer diseases will not be covered in this section, but readers are referred to other references for this information (Merritt, 2003; Papich, 1993; Matz, 1995; Henderson and Webster, 2006a, 2006b; Feldman and Burton, 1990).

Table 46.3 Antiulcer drugs: clinical uses

Gastritis
Gastric ulcers
Duodenal ulcers
Gastrointestinal ulcer prevention
Esophagitis
Mast cell tumors
Hypergastrinemic syndromes
Prevention and treatment of NSAID-induced ulcers

Because many of the ulcerative diseases encountered in veterinary medicine are induced by drugs that inhibit prostaglandin synthesis (nonsteroidal antiinflammatory drugs, NSAIDs), one should be familiar with the role of prostaglandins in the GI tract, how their synthesis is inhibited, and treatments used to maintain the protective effect of prostaglandins in the GI tract. Veterinarians also should be familiar with the normal physiological role of protective mucus layer in the stomach, the cytoprotective mechanisms, role of bicarbonate secretion, and the normal mechanisms that restore epithelial cells in the stomach and intestine. These factors were reviewed by Allen et al. (1993) several years ago, but are still relevant today. When these protective factors become disrupted or compromised, ulcers can occur in animals. Gastrointestinal ulcers are a major health problem in horses, pigs, dogs, cats, and zoo animals. Conditions that increase the risk of gastrointestinal ulceration are administration of ulcerogenic drugs (NSAIDs, corticosteroids, and stomach irritants), stress, disrupted mucosal blood supply, and inflammatory diseases.

Gastrointestinal ulceration is an important medical problem in horses, in which the prevalence in animals involved in showing and racing has been listed as 81–93%, and even as high as 100% in some studies. In Thoroughbreds and Standardbreds the prevalence is was 80–95%; and in show horses it may be as high as 58%. Factors such as stall confinement, intense exercise, diet (high energy concentration in diet), and racing stress may be contributing factors. Location of ulcers in horses is primarily in the squamous epithelium (nonglandular portion). Factors that contribute to ulcers are the intermittent feeding schedule and high stomach acidity. In sick foals, ulcers also are common. Factors that contribute to ulcers in foals are NSAIDs, stress, and sepsis.

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