40 Drugs Used in Gastrointestinal Disorders

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DRUG LIST

INTRODUCTION TO NORMAL PHYSIOLOGY

The gastrointestinal (GI) tract consists of the esophagus, stomach, small intestine, and colon. It processes ingested boluses of food and drink and expels waste material. Intervention by disease or pharmacological therapy may alter function of the GI tract. This chapter discusses drugs employed in the treatment of several GI disorders, emphasizing disease pathophysiology and drug mechanisms of action.

From the mid esophagus to the anus, smooth muscle surrounds the alimentary canal and is responsible for active movement and segmentation of intestinal contents. This smooth muscle, which lies in the muscularis propria, consists of a circular and a longitudinal layer of muscle.

From the gastric body to the colon, repetitive spontaneous depolarizations originate in the interstitial cells of Cajal, from which they spread to the circular muscle layer and then to the longitudinal muscle layer. The rate of slow-wave contraction varies in different regions of the gastrointestinal tract, occurring approximately 3 per minute in the stomach, 12 per minute in the proximal intestine, and 8 per minute in the distal intestine. The increased frequency of contraction in the proximal intestine forms a gradient of contraction, and intestinal contents are therefore propelled distally. Though the stomach has fewer spontaneous contractions than does the small intestine, there is normally no retrograde spread of a depolarization wave from duodenum to stomach.

The underlying intrinsic smooth muscle motility is modulated by neurohormonal influences. Afferent sensory neurons, extrinsic motor neurons, and intramural neurons innervate the gut. It also has mucosal sensory receptors for monitoring chemical, osmotic, or painful stimuli and muscle receptors to monitor degrees of stretch.

Both the parasympathetic and sympathetic nervous systems provide extrinsic gastrointestinal innervation. Parasympathetic stimulation increases muscle contraction of the gut, while sympathetic stimulation inhibits contractions. Stimulation of either α- or β-adrenoceptors will result in inhibition of contractions. The intramural nervous system consists of a myenteric (Auerbach's) plexus between the circular and longitudinal muscle areas and a submucosal (Meissner's) plexus between the muscularis mucosa and the circular muscle layers. *These two plexuses contain stimulatory cholinergic neurons.*

Ingested liquids are rapidly emptied from the stomach into the intestine, while digestible solids are first mechanically broken down in the stomach by peristaltic contractions. Stimulation of osmotic, carbohydrate, and fat receptors in the small bowel inhibits gastric peristaltic contractions and retards gastric emptying.

The small intestinal motility in the fed state consists of random slow-wave contractions that result in slow transit and long contact of food with enzymes and absorptive surfaces. With fasting, an organized peristaltic wave, termed the interdigestive *migrating motor complex,* begins to cycle every 84 to 112 minutes. During the migrating motor complex, a peristaltic contraction ring travels from the stomach to the cecum at 6 to 8 cm per minute. In the stomach the contractions sweep against a widely patent pylorus, permitting the passage of undigestible solids. In the small intestine this is to clear the intestine of undigested material: it functions as an intestinal housekeeper. The migrating motor complex appears to correlate with *motilin* hormonal levels and is modulated by vagal innervation. Motilin is a 22–amino acid polypeptide released from the duodenal mucosa as a regulator of normal GI motor activity. Exogenous motilin is a potent inducer of gastric motor activity.

Colonic motor function also has cyclic slow waves in the proximal colon. These contractions are primarily retrograde in the proximal colon, allowing segmentation and liquid reabsorption. In the distal colon a propulsive mass movement occurs intermittently. This may be stimulated by food ingestion and is termed the *gastrocolonic reflex.*

Approximately 1 to 1.5 L of fluid is ingested per day, and coupled with secretions from the stomach, pancreas, and proximal duodenum, approximately 8 L of chyme enters the jejunum per day. Reabsorption of 6 to 7 L occurs within the small bowel, leaving a residual of 1.5 L fluid, 90% of which is reabsorbed in the colon. This pattern of liquid reabsorption permits the elimination of fecal waste containing an average of 0.1 to 0.2 L fluid per day. *Diarrhea* occurs if there is an altered rate of intestinal motility, if mucosal function or permeability is altered, or if the fluid load entering the colon overwhelms colonic reabsorption. *Constipation* may occur if intestinal movement is inhibited or if there is a fixed obstruction.

DRUGS THAT INCREASE GI MOTILITY

Decreased GI motility can affect one or more parts of the GI tract and can be the result of a systemic disease, intrinsic GI disorder, or medication. *Gastroparesis* is the term for delayed gastric emptying. Symptoms may range from postprandial bloating and fullness to nausea and vomiting. Half of ingested liquid should be emptied within 30 minutes, and half of a digestible solid should be emptied within 2 hours. Emptying time can be prolonged as a result of autonomic neuropathy seen with

long-standing diabetes mellitus. Pseudoobstruction due to an idiopathic intestinal muscle disease or intestinal neuropathy may also cause delays in gastric emptying and intestinal transit. Rarer causes of delayed GI motility include Chagas' disease, muscular dystrophy, scleroderma, and infiltrative diseases, such as amyloidosis. Decreased GI transit can occur acutely following electrolyte disorders and gastroenteritis. In addition, many medications, including anticholinergic medications, tricyclic antidepressants, levodopa, and β-adrenergic agonists, inhibit GI motility.

Drugs that enhance GI motility are often called *prokinetics*. Their goal is to increase contractile force and accelerate intraluminal transit. Most of these drugs act either by enhancing the effect of acetylcholine or by blocking the effect of an inhibitory neurotransmitter such as dopamine. The prokinetics discussed in this chapter are metoclopramide, cisapride and tegaserod, and erythromycin.

Metoclopramide Hydrochloride

Metoclopramide (*Reglan*) stimulates upper GI tract motility and has both central and peripheral actions. Centrally, it is a dopamine antagonist, an action that is important both for its often desirable *antiemetic* effect and other less desirable effects. Peripherally, it stimulates the release of intrinsic postganglionic stores of acetylcholine and sensitizes the gastric smooth muscle to muscarinic stimulation. The ability of metoclopramide to antagonize the inhibitory neurotransmitter effect of dopamine on the GI tract results in increased gastric contraction and enhanced gastric emptying and small bowel transit.

Metoclopramide is rapidly absorbed following an oral dose in a patient with intact gastric emptying. Peak plasma concentration is achieved within 40 to 120 minutes. With normal renal function, plasma half-life is about 4 hours. About 20% of an oral dose is eliminated unchanged in the urine, while 60% is eliminated as sulfate or glucuronide conjugates.

Improved gastric emptying will frequently alleviate symptoms in patients with diabetic, postoperative, or idiopathic gastroparesis. Since metoclopramide also can decrease the acid reflux into the esophagus that results from slowed gastric emptying or lower esophageal sphincter pressure, the drug can be used as an adjunct in the treatment of reflux esophagitis.

Side effects include fatigue, insomnia, and altered motor coordination. Parkinsonian side effects and acute dystonic reactions also have been reported. Metoclopramide stimulates prolactin secretion, which can cause galactorrhea and menstrual disorders. Extrapyramidal side effects seen following administration of the phenothiazines, thioxanthenes, and butyrophenones may be accentuated by metoclopramide.

Cisapride and Tegaserod

Cisapride (*Propulsid*) and tegaserod (*Zelnorm*) are both serotonin-4 (5-HT_4) receptor agonists that stimulate GI motility. Cisapride appears to act by facilitating the release of acetylcholine from the myenteric plexus. It has no antiadrenergic, antidopaminergic, or cholinergic side effects. Following oral administration, peak plasma levels occur in 1.5 to 2 hours; the drug's half-life is 10 hours. Cisapride has been successfully used to treat gastroparesis and mild gastroesophageal reflux disease. The most frequent side effect has been diarrhea. A few patients had seizure activity that was reversible after medication was discontinued. Cisapride was pulled from the U. S. market after deaths from drug-associated cardiac arrhythmias, including ventricular tachycardia, ventricular fibrillation, torsades de pointes, and QT prolongation.

Tegaserod is being developed as a treatment for constipation-predominant irritable bowel syndrome (IBS). Within the first week, patients treated with tegaserod had significant improvements in abdominal pain and discomfort, constipation, and overall well-being. Efficacy was maintained throughout the treatment period. Tegaserod also demonstrated significant improvements in the three bowel-related assessments (stool frequency, stool consistency, and straining) within the first week, and these improvements were sustained throughout the treatment period. The most common adverse events reported thus far are headache and diarrhea.

Erythromycin

Erythromycin is an antibiotic in the macrolide family (see Chapter 47) that also has promotility effects because it is a motilin agonist. Erythromycin is used (off-label indication) to accelerate gastric emptying in diabetic gastroparesis and postoperative gastroparesis. Tachyphylaxis will occur, so it cannot be used uninterruptedly for long periods.

DRUGS THAT DECREASE GI MOTILITY

Diarrhea is the frequent passage of watery, unformed stools. Its many causes include IBS, infectious disorders, thyrotoxicosis, malabsorption, medication side effect, and laxative abuse. Attempts to treat diarrhea should first focus on the patient's list of medications followed by a search for an underlying systemic disorder. Opioids and 5-HT_3 receptor antagonists, such as alosetron, slow motility and can therefore decrease or eliminate diarrhea.

Opioids

Most of the opioids have a constipating action; morphine was used in the treatment of diarrhea before it

was used as an analgesic. Unfortunately, many of the opium preparations, while relieving diarrhea and dysentery, also produce such objectionable side effects as respiratory depression and habituation (see Chapter 26). *The opioids are capable of altering the motility pattern in all parts of the GI tract.* These compounds usually produce an increase in segmentation and a decrease in the rate of propulsive movement. The feces become dehydrated as a result of their longer stay in the GI tract. The tone of the internal anal sphincter is increased, and the subjective response to the stimulus of a full rectum is reduced by the central action of the opioids. All of these actions produce constipation. Opioids should not be used indiscriminately in bloody diarrhea, since their use in inflammatory bowel disease involving the colon may increase the risk of megacolon and their use in infectious enterocolitis may promote intestinal perforation.

The dangers of dependency and addiction clearly preclude the use of such compounds as morphine, meperidine, and methadone as treatment for diarrhea. Antidiarrheal specificity therefore is of paramount importance in choosing among the synthetic opioids and their analogues (e.g., diphenoxylate and loperamide).

Diphenoxylate (marketed in combination with atropine as *Lomotil* in the United States) is chemically related to both analgesic and anticholinergic compounds. It is as effective in the treatment of diarrhea as the opium derivatives, and at the doses usually employed, it has a low incidence of central opioid actions. Diphenoxylate is rapidly metabolized by ester hydrolysis to the biologically active metabolite difenoxylic acid. Lomotil is recommended as adjunctive therapy in the management of diarrhea. It is contraindicated in children under 2 years old and in patients with obstructive jaundice. Adverse reactions often caused by the atropine in the preparation include anorexia, nausea, pruritus, dizziness, and numbness of the extremities.

Loperamide hydrochloride (*Imodium*) structurally resembles both haloperidol and meperidine. In equal doses, loperamide protects against diarrhea longer than does diphenoxylate. It reduces the daily fecal volume and decreases intestinal fluid and electrolyte loss. Loperamide produces rapid and sustained inhibition of the peristaltic reflex through depression of longitudinal and circular muscle activity. The drug also possesses antisecretory activity, presumably through an effect on intestinal opioid receptors. Loperamide is effective against a wide range of secretory stimuli and can be used in the control and symptomatic relief of acute diarrhea that is not secondary to bacterial infection. Adverse effects associated with its use include abdominal pain and distention, constipation, dry mouth, hypersensitivity, and nausea and vomiting.

Tincture of opium (10% opium) is a rapidly acting preparation for the symptomatic treatment of diarrhea. The more widely used paregoric (camphorated opium tincture) is equally effective and is frequently used in combination with other antidiarrheal agents. Codeine also has been used for short-term symptomatic treatment.

Alosetron

Alosetron (*Lotronex*) is a 5-HT_3 receptor antagonist. Blocking this receptor results in decreased GI motility. Alosetron received FDA approval in February 2000 for the treatment of women with diarrhea-predominant IBS. In November 2000, at the request of the FDA, the drug was voluntarily withdrawn due to reported cases of ischemic colitis, including some fatalities.

PHARMACOLOGICAL MODULATION OF DIARRHEA AND CONSTIPATION BY MECHANISMS THAT DO NOT DIRECTLY AFFECT MOTILITY

Drugs Useful for Treating Diarrhea: Adsorbents and Bulking Agents

Kaolin powder and other hydrated aluminum silicate clays, often combined with pectin (a complex carbohydrate), are the most widely used adsorbent powders (e.g., *Kaopectate*). Kaolin is a naturally occurring hydrated aluminum silicate that is prepared for medicinal use as a very finely divided powder. The rationale behind its use in acute nonspecific diarrhea stems from its ability to adsorb some of the bacterial toxins that often cause the condition. It is almost harmless and is effective in many cases of diarrhea if taken in large enough doses (2–10 g initially, followed by the same amount after every bowel movement). The adsorbents are generally safe, but they may interfere with the absorption of some drugs from the GI tract.

Bismuth subsalicylate (*Pepto-Bismol*) also binds intestinal toxins and may coat irritated mucosal surfaces. This compound is a salicylate and may therefore produce signs of salicylate toxicity (e.g., ringing of the ears) if taken chronically, especially with aspirin. Bismuth is radiopaque and may interfere with radiological examinations. Its use may cause temporary gray-black discoloration of the stool and brown pigmentation of the tongue. High dose Pepto-Bismol (8 tablets/day) has been efficacious in some patients with diarrhea secondary to collagenous or lymphocytic colitis.

Hydrophilic substances such as calcium polycarbophil (*FiberCon, Equalactin*), methylcellulose (*Citrucel*), and various psyllium seed derivatives (*Metamucil*) are natural or synthetic fiber supplements that bind water and bile salts and may be useful in controlling diarrhea associated with the passing of excessively watery stools.

Drugs Useful for Treating Constipation

There is a great deal of variability in bowel habits from person to person; a normal stool frequency may vary from three stools per week up to three stools per day. Constipation is defined as the infrequent passage of stool. It may be secondary to sluggish colonic motility, in which soft stool is seen throughout the colon, or to difficulties with evacuation in which firm stool is seen primarily in the sigmoid and rectum.

The dangers of excessive purging are salt and fluid loss and gradually increasing desensitization of the bowel to normal stimuli; the latter effect forces the cathartic user to employ larger and larger doses.

Laxatives are used to increase stool frequency and reduce stool viscosity. Even with long-term use, bulk laxatives and pure osmolar laxatives do not predispose patients to formation of a cathartic-type colon and should be the initial agents used for chronic constipation after a structural obstructing lesion has been excluded. Laxatives are also used before radiological, endoscopic, and abdominal surgical procedures; such preparations quickly empty the colon of fecal material. Nonabsorbable hyperosmolar solutions or saline laxatives are used for this purpose. Classification and comparison of representative laxatives are provided in Table 40.1.

Stool Softeners

Fecal softeners are substances that are not absorbed from the alimentary canal and act by increasing the bulk of the feces and softening the stool so that it is easier to pass. Mineral oil has been in use for many years, either as the oil or as a white emulsion; it is a mixture of liquid hydrocarbons. Its use has been criticized for many reasons. It dissolves the fat-soluble vitamins and prevents their absorption. It is itself absorbed slightly and appears in the mesenteric lymph nodes, and if it is inhaled into the lungs (which it may be in elderly or debilitated patients), it may produce inflammatory responses such as lipoid pneumonia. Its continual use, therefore, is contraindicated, although its occasional administration in otherwise well patients is not harmful. It is employed primarily in patients who must avoid straining at stool, including persons with hemorrhoids and other painful anal lesions. Leakage of mineral oil past the anal sphincter may lead to soiling of clothing.

Docusate dioctyl sodium sulfosuccinate (*Colace*), dioctyl calcium sulfosuccinate (*Surfak*), and dioctyl potassium sulfosuccinate (*Diocto-K*) are surface-active agents that produce fecal softening in 1 or 2 days. By means of its detergent properties, docusate allows water to penetrate and soften colonic contents when it is administered as a retention enema. Orally ingested docusate may also act as a stool softener by stimulating the secretion of water and electrolytes into the intestinal lumen. Docusate has been used both alone and in combination with other laxatives. Although by itself it appears to be relatively nontoxic, it may, when taken in combination with other laxatives, increase their absorption and lead to liver toxicity. Caution is necessary when docusate is prescribed together with mineral oil, since the detergent increases the absorption of the oil.

Bulk Forming Laxatives

The bulk-forming laxative group includes the hydrophilic substances described previously: calcium polycarbophil (*FiberCon, Equalactin*), methylcellulose (*Citrucel*), and various psyllium seed derivatives (*Metamucil*). All act by increasing the bulk of the feces, part of this action being due to their capacity to attract water and form a hydrogel. The increased volume of feces stretches the walls of the GI tract and stimulates peristalsis. Their action may not be evident for 2 to 3 days after starting treatment. Because their use results

TABLE 40.1 Classification and Comparison of Representative Laxatives: Type, Cathartic Effect, and Latency

Softening of Formed Stool (1–3 d)	Soft, Semifluid Stool (6–12 hr)	Watery Stool (2–6 hr)
Bulk-forming agents	Saline laxatives (low dose)	Saline laxatives (high dose)
Dietary fiber	Milk of magnesia	Magnesium citrate
Methylcellulose	Magnesium sulfate	Magnesium sulfate
Psyllium	Diphenylmethane derivatives	Sodium phosphates
Calcium polycarbophil	Phenolphthalein	Castor oil
Docusate salts	Bisacodyl	Polyethylene glycol–electrolyte preparations
Sodium, potassium, or calcium salts of dioctyl sulfosuccinate	Anthraquinone derivatives	
Lactulose	Senna	
Sorbitol	Cascara sagrada	
Polyethylene glycol		

Adapted with permission from AMA Drug Evaluations (6th Ed.). Chicago: American Medical Association, 1986.

in increased water content in the feces, the patient should be advised to drink adequate amounts of water; otherwise dehydration may result.

The use of *high-fiber diets* has recently received a great deal of publicity, and many claims have been made for the value of such diets. Fiber in the diet is derived entirely from plant material, either from fruit and vegetables or from cereals, the latter being known as *bran*. The fiber content in each case is a complex carbohydrate in the form of cellulose, pectin, and lignin. These fibers pass through the human GI tract relatively unaltered by enzymes.

A high-fiber diet is effective in the prevention of constipation and diverticulitis. Claims also have been made that such diets prevent cancer of the colon. Such allegations require further study.

Since clear advantages accrue from a high-bran diet (a reduction in both constipation and diverticulitis) and since there is no associated toxicity, *a bulk-forming laxative is the laxative of choice for constipated patients.*

Osmotic Laxatives

Osmotic laxatives (e.g., lactulose, sorbitol) are poorly absorbed or nonabsorbable compounds that draw additional fluid into the GI tract. Lumen osmolality increases, and fluid movement occurs secondary to osmotic pressure. Lactulose is a synthetic disaccharide that is poorly absorbed from the GI tract, since no mammalian enzyme is capable of hydrolyzing it to its monosaccharide components. It therefore reaches the colon unchanged and is metabolized by colonic bacteria to lactic acid and to small quantities of formic and acetic acids. Since lactulose does contain galactose, it is contraindicated in patients who require a galactose-free diet. Metabolism of lactulose by intestinal bacteria may result in increased formation of intraluminal gas and abdominal distention. Lactulose is also used in the treatment of hepatic encephalopathy.

Polyethylene glycol (*Miralax*) is another osmotic laxative that is colorless and tasteless once it is mixed.

Saline Laxatives

Saline laxatives are soluble inorganic salts that contain multivalent cations or anions (milk of magnesia, magnesium citrate, and sodium phosphate [*Fleet Phospho Soda*]). These charged particles do not readily cross the intestinal mucosa and therefore tend to remain in the lumen of the GI tract, where they help retain fluid through the osmotic effect exerted by the unabsorbed ions. The volume in the GI tract is increased, distending the colon and producing a physiological stimulus for peristalsis through activation of stretch receptors. This explanation of the mechanism by which the saline laxatives exert their effects, however, may be too simplistic, since active secretion of fluid into the gut lumen has been documented following the administration of magnesium-containing agents.

These salts should always be given with substantial amounts of water; otherwise the patient may be purged at the expense of body water, resulting in dehydration. Sodium-containing laxatives should not be used in patients with congestive heart failure, since the patient may absorb excessive sodium. Similarly, in cases of renal failure, magnesium or phosphate-containing products should not be used, since the loss of a renal clearance of these ions may result in cumulative toxic levels despite their minimal absorption.

Enemas may contain water, salts, soap, mineral detergent (docusate potassium), or hypertonic (sorbitol, sodium phosphate–biphosphate) fluids. These are convenient and generally safe for short-term use. Many of these solutions irritate the mucosa and may produce excessive mucus in the stool. Excessive use of these enema products may result in water intoxication and hyponatremia.

A new formulation of a saline laxative, *Visicol*, that is useful to prepare patients for procedures, was approved for use in 2001. Each 2-g tablet contains 1.102 g sodium phosphate monobasic monohydrate and 0.398 g sodium phosphate dibasic anhydrous, for a total of 1.5 g sodium phosphate. Visicol tablets, taken in two doses of 30 g approximately 12 hours apart, induce diarrhea that rapidly and effectively cleanses the entire colon. Each administration has a purgative effect for approximately 1 to 3 hours.

Stimulant Cathartics

The stimulant cathartics contain a variety of drugs whose exact mode of action is not known, although it is thought that they act on the mucosa of the intestine to stimulate peristalsis either by irritation or by exciting reflexes in the myenteric plexuses. All act in the lumen of the GI tract and are inactive if given parenterally. They produce irritation of the mucosa if given in large doses, and this irritation affects water and ion transport. However, a direct local irritation may not be essential to their action. It has been suggested that these drugs may act by stimulating afferent nerves to initiate a reflex increase in gut motility.

Anthraquinone derivatives (e.g., cascara, aloe, senna, and rhubarb) are among the oldest laxatives known. They act on the colon rather than on the ileum and produce evacuation 8 to 10 hours after administration. This makes them particularly suitable for dosage overnight. Cascara sagrada is one of the mildest of the anthraquinone-containing laxatives.

Phenolphthalein is partially absorbed (about 15% of a given dose) and excreted into the bile; hence, if it is taken constantly, it will accumulate and exert too drastic an action. It inhibits active sodium and glucose

absorption in the bowel. Once widely available in many over-the-counter products, it was pulled from the market when it was linked to cancer.

Castor oil is a bland oil that is hydrolyzed in the gut to yield ricinoleic acid, the active purging agent. This hydrolysis requires bile, a fact that is sometimes overlooked when castor oil is given as a laxative before radiography in biliary obstruction. The ricinoleic acid acts on the ileum and colon to induce an increased fluid secretion and colonic contraction.

Bisacodyl (*Dulcolax*) causes colonic contraction and inhibits water absorption in the small and large intestine.

Isoosmotic Electrolyte Colonic Lavage Solutions

Electrolyte colonic lavage solutions (e.g., *GoLYTELY, Colyte, Nulytely*) contain polyethylene glycol and salts such as sodium sulfate, sodium bicarbonate, sodium chloride, and potassium chloride in an isoosmotic solution. The dose is 4 L ingested over 2 to 4 hours either orally or through a nasogastric tube. There is minimal net absorption or excretion of fluid or electrolytes, and thus these are safe to use in patients with renal insufficiency. The patient has repeated liquid stools until the administered solution has been expelled. If gastric emptying is slow, patients may have abdominal distention with vomiting. This preparation should not be used if a bowel obstruction or impaired gag reflex is present. It is used primarily to clear the bowel before radiological or endoscopic procedures and occasionally to assist with evacuation in a patient who has a sluggish colon.

PHARMACOLOGICAL MODULATION OF VOMITING

Vomiting is a complex series of integrated events culminating in the forceful expulsion of gastric contents through the mouth. The sequence of events frequently begins with nausea, which may be accompanied by increased salivation, pupillary dilation, sweating, and pallor. Duodenal and jejunal tone is increased, while gastric tone and peristalsis are diminished, tending to cause a reflux of duodenal contents into the stomach. Retching follows nausea, during which the abdominal muscles contract with simultaneous attempts at inspiration against a closed glottis. The gastric antrum contents and gastric contents begin to move into the esophagus. During vomiting, which is the third and final stage, there is sustained contraction of the diaphragm and abdominal musculature. The resultant high intragastric pressure moves more gastric contents into the esophagus, and with continued force, contents are expelled through the mouth.

These events are coordinated by the *emetic center,* which lies within the lateral reticular formation of the medulla oblongata close to the respiratory and salivary centers. Stimulation of the emetic center may occur from peripheral sites, the cortex, or the *chemoreceptor trigger zone* (CTZ). Peripheral stimulation, which is mediated by vagal and sympathetic nerves, may originate from the vestibular system (motion sickness), from the coronary arteries (cardiac ischemia), or from distention and inflammation of sites in the GI tract.

The CTZ, which is responsive to chemical (particularly dopamine) stimulation, is connected to the emetic center through the fasciculus solitarius. Most drug-induced emesis, including emesis induced by apomorphine, levodopa, cardiac glycosides, most cancer chemotherapeutic agents, and nicotine, appears to be mediated by this route. Cytotoxic chemotherapy also stimulates the release of serotonin from enterochromaffin cells of the upper GI tract. Vomiting may then be induced through serotonergic stimulation of enteric vagal afferents or possibly through direct central nervous system stimulation.

Emetics

The most commonly used emetics are ipecac and apomorphine. Induced emesis is the preferred means of emptying the stomach in awake patients who have ingested a toxic substance or have recently taken a drug overdose. Emesis should not be induced if the patient has central nervous system depression or has ingested certain volatile hydrocarbons and caustic substances.

Ipecac syrup is prepared from the dried rhizome and roots of *Cephaelis ipecacuanha* or *Cephaelis acuminata,* plants from Brazil and Central America that have the alkaloid *emetine* as their active principal ingredient. It acts directly on the CTZ and also indirectly by irritating the gastric mucosa. Ipecac is cardiotoxic if absorbed and can cause cardiac conduction disturbances, atrial fibrillation, or fatal myocarditis. If emesis does not occur, gastric lavage using a nasogastric tube must be performed.

Apomorphine, a derivative of morphine, acts directly on the CTZ. It also is more effective if water is first administered before oral or subcutaneous dosing. Excessive dosage may cause respiratory depression and circulatory collapse. Opioid antagonists such as naloxone usually reverse the depressant actions of apomorphine. Because of the possibility of respiratory depression, apomorphine is infrequently used as an emetic.

Antiemetics

Antiemetics may prevent emesis by blocking the CTZ or by preventing peripheral or cortical stimulation of the emetic center.

Antihistamines

The antihistamines appear to block peripheral stimulation of the emetic center. They are therefore most ef-

fective in motion sickness and inner ear dysfunction, as is seen in Ménière's syndrome, labyrinthitis, and streptomycin ototoxicity. Dimenhydrinate, diphenhydramine, and meclizine hydrochloride are the three antihistamines primarily used in the prevention of nausea from inner ear stimulation. A more complete discussion of the H_1 antihistamines can be found in Chapter 38.

Anticholinergics

The transdermal adhesive form of scopolamine (*Transderm Scop*) provides up to 72 hours of antiemetic protection when applied to the postauricular area. Side effects are similar to those of oral scopolamine (see Chapter 13) but milder.

Benzodiazepines

Benzodiazepines and their congeners may help prevent central cortical-induced vomiting. A prominent side effect is drowsiness. They are frequently used in combination with other antiemetics for treating chemotherapy-related nausea and vomiting. Discussion of these agents is found in Chapter 30.

Cannabinoids

The antiemetic site of action of tetrahydrocannabinol (THC) (*Marinol*) is unknown, although it appears to affect the central cerebral cortex axis. Relief may occur in individuals refractory to other antiemetics. It is less effective in the elderly, primarily because of its side effects. The antiemetic effect is associated with a high, and this appears to be better tolerated in the young. Sedation is seen in approximately 30% of patients. Ataxia, drowsiness, dry mouth, or orthostatic hypotension may be seen in up to 35% of the older patient population. GI absorption is variable, though blood levels correlate with efficacy. The bioavailability is not as variable if the agent is smoked. The coadministration of prochlorperazine may prevent some of the central nervous system side effects seen with the use of tetrahydrocannabinol.

Dopamine Antagonists

Metoclopramide is a dopamine antagonist that centrally inhibits stimulation of the CTZ. By improving gastric emptying, it can decompress the stomach, thereby decreasing a peripherally associated stimulation of the emetic center. Metoclopramide may precipitate extrapyramidal reactions and sedation. For further details, see earlier section, Drugs that Increase GI Motility.

Phenothiazine Derivatives

Phenothiazine derivatives, which include prochlorperazine (*Compazine*) and promethazine (*Phenergan*), act at the CTZ by inhibiting dopaminergic transmission. They also decrease vomiting caused by gastric irritants, suggesting that they inhibit stimulation of peripheral vagal and sympathetic afferents. Sedation will frequently occur following their administration. Patients also may have problems with acute dystonic reactions, orthostatic hypotension, cholestatic hepatitis, and blood dyscrasias.

5-HT_3 Receptor Antagonists

Ondansetron (*Zofran*) and granisetron (*Kytril*) are potent antagonists of 5-HT_3 receptors, which are found peripherally on vagal nerve terminals and centrally in the CTZ. During chemotherapy that induces vomiting, mucosal enterochromaffin cells in the GI tract release serotonin, which stimulates 5-HT_3 receptors. This causes vagal afferent discharge, inducing vomiting. In binding to 5-HT_3 receptors, ondansetron and granisetron block serotonin stimulation, hence vomiting, after emetogenic stimuli such as cisplatin. Headache is the most frequently reported adverse effect of these medications.

DRUGS THAT DECREASE OR NEUTRALIZE GASTRIC ACID SECRETION

Functionally, the gastric mucosa is divided into three areas of secretion. The *cardiac gland area* secretes mucus and pepsinogen. The *oxyntic (parietal) gland area,* which corresponds to the fundus and body of the stomach, secretes hydrogen ions, pepsinogen, and bicarbonate. The *pyloric gland area* in the antrum secretes gastrin and mucus.

The parietal cells secrete H^+ in response to gastrin, cholinergic, and histamine stimulation (Fig. 40.1). Both cholinergic- and gastrin-induced types of stimulation bring about a receptor-mediated rise in intracellular calcium, an activation of intracellular protein kinases, and eventually an increased activity of the H^+–K^+ pump leading to acid secretion into the gastric lumen. Following histamine stimulation, a guanine nucleotide–binding protein (G_s) activates adenylyl cyclase, leading to an increase in intracellular levels of the second messenger, cyclic adenosine monophosphate (cAMP). Activation of cAMP-dependent protein kinases initiates the stimulation of the H^+–K^+ pump.

The cephalic–vagal axis, gastric distention, and local mucosal chemical receptors can modulate acid secretion by the stomach. The smell, taste, sight, or discussion of food may result in cephalic–vagal postganglionic cholinergic stimulation of target parietal cells and enhanced antral gastrin release. After food is ingested, gastric distention initiates vagal stimulation and short intragastric neural reflexes, both of which increase acid secretion. Proteins in ingested meals also stimulate acid

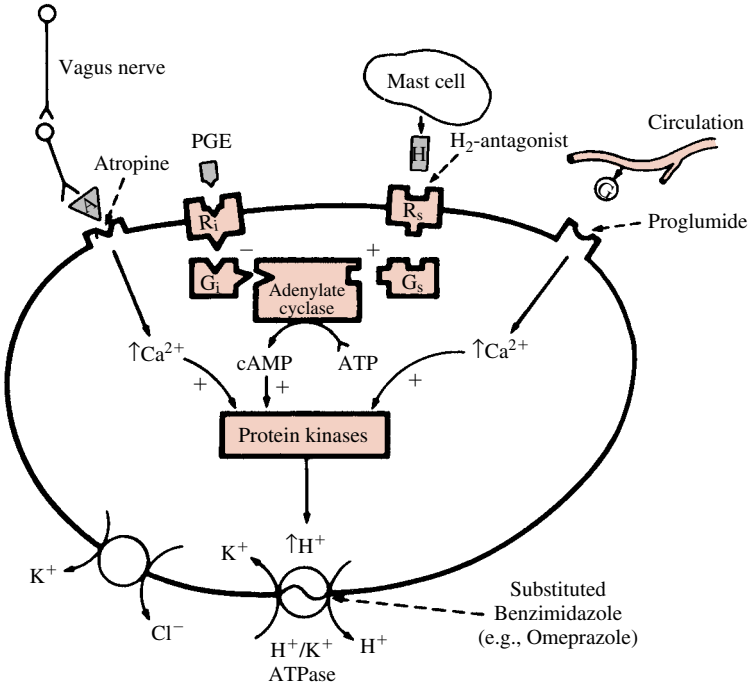

FIGURE 40.1
Influences on parietal cell acid secretion. The pathways by which secretagogues are believed to stimulate hydrogen ion production and secretion are shown. In addition, the sites of action (broken arrows) of various acid suppressive medications are shown. A, atropine; PGE, prostaglandin E; H, histamine; G, gastrin, R_i and R_s, inhibitory and stimulatory receptor-binding sites; G_i and G_s, inhibitory and stimulatory catalytic subunits; ATP, adenosine triphosphate; ATPase, adenosine triphosphatase. (Reprinted with permission from Wolfe MM and Soll AH. The physiology of gastric acid secretion. N Engl J Med 1988;319:1707.)

secretion. Evidence from animal studies suggests that after protein amino acids are converted to amines, gastrin is released.

Gastric acid secretion is inhibited in the presence of acid itself. A negative feedback occurs when the pH approaches 2.5 such that further secretion of gastrin is inhibited until the pH rises. Ingested carbohydrates and fat also inhibit acid secretion after they reach the intestines; several hormonal mediators for this effect have been proposed. The secretion of pepsinogen appears to parallel the secretion of H^+, while the patterns of secretion of mucus and bicarbonate have not been well characterized.

The integrity of the mucosal lining of the stomach and proximal small bowel is in large part determined by the mucosal cytoprotection provided by mucus and bicarbonate secretion from the gastric and small bowel mucosa. Mucus retards diffusion of the H^+ from the gastric lumen back into the gastric mucosal surface. In addition, the bicarbonate that is secreted into the layer between the mucus and epithelium permits a relatively high pH to be maintained in the region next to the mucosal surface. If any H^+ does diffuse back to the level of the mucosal surface, both the local blood supply and the ability of the local cells to buffer this ion will ultimately determine whether peptic ulceration will occur. With duodenal and gastric peptic ulcer disease, a major causative cofactor is the presence of gastric *Helicobacter pylori* infection.

Medications that raise intragastric pH are used to treat peptic ulcer disease and gastroesophageal reflux disease. In addition, agents that enhance mucosal cytoprotection are used to decrease ulcer risk.

Antacids

The rationale for the use of antacids in peptic ulcer disease lies in the assumption that buffering of H^+ in the stomach permits healing. The use of both low and high doses of antacids is effective in healing peptic ulcers as compared with placebo. Healing rates are comparable with those observed after the use of histamine (H_2) blocking agents. The buffering agents in the various antacid preparations consist of combinations of ingredients that include sodium bicarbonate, calcium carbonate, magnesium hydroxide, and aluminum hydroxide. If

diarrhea occurs or if there is renal failure, a magnesium-based preparation should be discontinued. The agents are generally safe, but some patients resist because some of the formulations are unpalatable and expensive.

A variety of adverse effects have been reported following the use of antacids. If sodium bicarbonate is absorbed, it can cause systemic alkalization and sodium overload. Calcium carbonate may induce hypercalcemia and a rebound increase in gastric secretion secondary to the elevation in circulating calcium levels. Magnesium hydroxide may produce osmotic diarrhea, and the excessive absorption of Mg^{++} in patients with renal failure may result in central nervous system toxicity. Aluminum hydroxide is associated with constipation; serum phosphate levels also may become depressed because of phosphate binding within the gut. The use of antacids in general may interfere with the absorption of a number of antibiotics and other medications.

H_2-Receptor Antagonists

The histamine receptor antagonists (H_2 blockers) marketed in the United States are cimetidine (*Tagamet*), ranitidine (*Zantac*), famotidine (*Pepcid*), and nizatidine (*Axid*). These agents bind to the H_2-receptors on the cell membranes of parietal cells and prevent histamine-induced stimulation of gastric acid secretion. After prolonged use, down-regulation of receptor production occurs, resulting in tolerance to these agents. H_2-blockers are approved for the treatment of gastroesophageal reflux disease, acute ulcer healing, and post–ulcer healing maintenance therapy. Although there are substantial differences in their relative potency, 70 to 85% of duodenal ulcers are healed during 4 to 6 weeks of therapy with any of these agents. The incidence of healing of gastric ulceration after 6 to 8 weeks of therapy approaches 60 to 80% with the use of cimetidine or ranitidine. Since nocturnal suppression of acid secretion is particularly important in healing, nighttime-only dosing can be used. Most are available in low-dose over-the-counter formulations.

Cimetidine, the first released H_2-blocker, like histamine, contains an imidazole ring structure. It is well absorbed following oral administration, with peak blood levels 45 to 90 minutes after drug ingestion. Blood levels remain within therapeutic concentrations for approximately 4 hours after a 300-mg dose. Following oral administration, 50 to 75% of the parent compound is excreted unchanged in the urine; the rest appears primarily as the sulfoxide metabolite.

Cimetidine may infrequently cause diarrhea, nausea, vomiting, or mental confusion. A rare association with granulocytopenia, thrombocytopenia, and pancytopenia has been reported. Gynecomastia has been demonstrated in patients receiving either high-dose or long-term therapy. This occurs because cimetidine has a weak antiestrogen effect. Since cimetidine is partly metabolized by the cytochrome P450 system, coadministered drugs such as the benzodiazepines, theophylline, and warfarin, which are also metabolized by this system, may accumulate if their dosage is not adjusted.

Ranitidine is well absorbed after oral administration, with a peak plasma level achieved 1 to 3 hours after ingestion. Elimination is by renal (25%) and hepatic (50%) routes. The half-life of elimination is 2.5 to 3.0 hours. Nizatidine is the newest H_2-receptor antagonist. Similar to ranitidine, it has a relative potency twice that of cimetidine. About 90% of an oral dose is absorbed, with a peak plasma concentration occurring after 0.5 to 3 hours; inhibition of gastric secretion is present for up to 10 hours. The elimination half-life is 1 to 2 hours, and more than 90% of an oral dose is excreted in the urine. Famotidine has an onset of effect within 1 hour after oral administration, and inhibition of gastric secretion is present for the next 10 to 12 hours. It is the most potent H_2-blocker. Elimination is by renal (65–70%) and hepatic (30–35%) routes. Ranitidine, famotidine, and nizatidine do not alter the microsomal cytochrome P450 metabolism of other drugs, nor do they cause gynecomastia. A reduction in dosage of any of the H_2-blockers is recommended in the presence of renal insufficiency.

Proton Pump Inhibitors

The proton pump inhibitors available in the United States are omeprazole (*Prilosec*), lansoprazole (*Prevacid*), pantoprazole (*Protonix*), rabeprazole (*Aciphex*), and esomeprazole (*Nexium*). These are substituted benzimidazole prodrugs, which accumulate on the luminal side of parietal cells' secretory canaliculi. They become activated by acid transport and then bind covalently to the actual H^+–K^+ ATPase enzymes (proton pumps) irreversibly blocking them. *These drugs markedly inhibit gastric acid secretion.* New proton pumps are continuously formed, and thus no tolerance develops. Peptic ulcers and erosive esophagitis that are resistant to other therapies will frequently heal when these agents are used. The proton pump inhibitors are also used to treat patients with *Zollinger-Ellison syndrome,* which is the result of a gastrin-hypersecreting neuroendocrine tumor.

The prodrugs are unstable in the presence of acid and therefore must be administered as an enteric-coated preparation or as a buffered suspension. Pantoprazole is also available in an intravenous formulation. The most commonly reported side effects are diarrhea and headache. Hypergastrinemia has been noted as a reaction to the marked reduction in acid secretion. Gastric carcinoid tumors have developed in rats but not in mice or in human volunteers, even after long-term use.

TREATMENT OF INFLAMMATORY BOWEL DISEASE

Inflammatory bowel disease mainly refers to *ulcerative colitis* and *Crohn's disease.* Ulcerative colitis is characterized by a relapsing inflammatory condition involving the mucosa of variable lengths of the colon resulting in bleeding, urgency, diarrhea, and tenesmus. The endoscopic and radiographic appearance may demonstrate multiple diffuse erosions or ulcerations. Biopsy reveals distorted crypt abscesses and diminished goblet cells. When involvement is limited to the rectum, it is termed ulcerative proctitis. Crohn's disease may involve the gut from esophagus to anus; however, the small bowel or colon or both are the major areas of involvement. Inflammation is transmural. If the colon is predominantly involved, the symptoms and presentation are quite similar to those of ulcerative colitis. Small bowel involvement may result in large-volume bloodless diarrhea or obstruction. Normal areas of gut may be found between areas of inflamed mucosa. Fistulas, strictures, and abscess formation are fairly common in Crohn's disease.

The present primary mode of therapy for these diseases involves the use 5-amino-salicylate (5-ASA) products. Often patients require additional medications, including corticosteroids, to help induce remission and various immune modulators, such as azathioprine, 6-mercaptopurine or methotrexate, to maintain remission. In Crohn's disease certain antibiotics, such as metronidazole and ciprofloxacin, and infliximab (*Remicade*), an anti–tumor necrosis factor-α(TNFα) antibody, also have been used. The pharmacology of antibiotics, immunosuppressive drugs, and corticosteroids is discussed in Chapters 43, 57, and 60, respectively.

5-Aminosalicylates

Sulfasalazine (*Azulfidine*) was first introduced in 1940 as a treatment for rheumatoid arthritis. It was found that a number of patients with coexistent inflammatory bowel disease showed improvement of their GI symptoms, and the drug has subsequently been used for the treatment of patients with inflammatory bowel disease.

Sulfasalazine is composed of sulfapyridine and 5-ASA molecules linked by an azo bond. Sulfapyridine has no effect on the inflammatory bowel disease, and instillation of this agent into the colon does not heal colonic mucosa. It is, however, responsible for most of sulfasalazine's side effects, including sulfa allergic reactions. 5-ASA, the active metabolite, may inhibit the synthesis of mediators of inflammation.

Following oral administration, 30% of the sulfasalazine is absorbed from the small intestine. Because most of the compound that is absorbed is later excreted into the bowel, 75 to 85% of the administered oral dose eventually reaches the colon intact. Bacteria in the colon then split the azo linkage, liberating sulfapyridine and 5-ASA. The sulfapyridine is absorbed, acetylated, hydroxylated, and conjugated to glucuronic acid in the liver. The major portion of the sulfapyridine molecule and its metabolites are excreted in the urine. The 5-ASA remains in the colon, eventually reaching high fecal levels.

Sulfasalazine treatment results in an 85% remission rate in mild to moderate ulcerative colitis. Termination of therapy leads to an 80% relapse within the next year. In Crohn's disease, sulfasalazine acts primarily on involved colonic mucosa, although remission of ileal disease also has been reported. The National Cooperative Crohn's Disease Study found sulfasalazine to be better in the treatment of colonic disease, while corticosteroids were judged better in the treatment of small bowel disease. Since sulfasalazine does not prevent relapse of Crohn's disease once remission is achieved, maintenance therapy is not characteristically used.

Nausea, vomiting, and headaches, the most common side effects, are related to the blood level of sulfapyridine. If the dose is reduced, symptoms frequently improve. Fever, rash, aplastic anemia, and autoimmune hemolysis are hypersensitivity reactions to the medication. These occur less commonly and are not dose related. Sulfasalazine should not be used in patients with hypersensitivity agranulocytosis or aplastic anemia.

Since sulfasalazine inhibits the absorption of folic acid, patients may become folate deficient during long-term therapy. Sulfasalazine decreases the bioavailability of digoxin. Cholestyramine reduces the metabolism of sulfasalazine. Sulfasalazine causes a reversible decrease in sperm counts. Sulfasalazine is safe in pregnancy.

To avoid the side effects of sulfapyridine, various preparations to target 5-ASA directly to sites of disease have been formulated. Also known as mesalamine, 5-ASA has been formulated in oral forms (*Pentasa, Asacol*). Pentasa is a time-release capsule that releases the drug throughout the GI tract. Asacol is a pH-dependent–release preparation that delivers drug to the distal small bowel and colon. The response of ulcerative colitis to this formulation appears to be identical to that seen with sulfasalazine. Mesalamine can also be administered as a suppository (*Canasa*) or enema (*Rowasa*) for distal colonic disease.

Olsalazine sodium (*Dipentum*) links two 5-ASA molecules with an azo linkage. Following cleavage of the azo linkage in the colon, two 5-ASA molecules are released. Olsalazine is approved for maintenance of remission of ulcerative colitis, but a commonly reported side effect is a paradoxical increase in diarrhea. The U. S. Food and Drug Administration (FDA) has approved balsalazide disodium (*Colazal*) as a treatment of mild to moderately active ulcerative colitis. Balsalazide

disodium is delivered intact to the colon, where it is cleaved by bacterial azoreduction to release equimolar quantities of mesalamine, the therapeutically active portion of the molecule, and 4-aminobenzoyl-β-alanine; the latter compound is only minimally absorbed and is largely inert.

Infliximab

TNF-α is an inflammatory cytokine thought to have a contributory role in producing chronic inflammation in various diseases, including Crohn's disease and rheumatoid arthritis (see Chapter 36). Infliximab (*Remicade*) is a mouse–human chimeric monoclonal *neutralizing* antibody to human TNF-α and is considered a biological drug. Specific indications are for the reduction of signs and symptoms in patients with moderately to severely active Crohn's disease who have had an inadequate response to conventional therapies (single infusion) and for reduction of the number of draining enterocutaneous fistulas in patients with fistulizing Crohn's disease (three-infusion regimen). Responses occur within 2 weeks of an infusion, and significant clinical responses were reported in 50 to 80% of patients in initial trials with infliximab. This antibody is being studied as maintenance therapy for Crohn's disease and to determine the best induction regimen to achieve remission.

The most common side effects, which are related to the intravenous infusion itself, include rash, low blood pressure, chills, and chest pain. These symptoms are generally temporary and often respond to a decrease in infusion rate. In addition, some patients develop antibodies, which have been associated in rare cases with symptoms similar to those of patients with systemic lupus erythematosus. These symptoms were also temporary. Another side effect is increased risk of infections. Fatal cases of tuberculosis have been reported following infliximab therapy. Another potential side effect is an increased risk of lymphoma. Its occurrence remains controversial.

Budesonide

Recently, budesonide (*Entecort EC*) has been approved for the treatment of mildly to moderately active Crohn's disease involving the ileum and/or ascending colon. Budesonide is a synthetic corticosteroid having a potent glucocorticoid and weak mineralocorticoid activity. In standard in vitro and animal models, budesonide has an approximately 200-fold higher affinity for the glucocorticoid receptor and a 1000-fold higher topical antiinflammatory potency than cortisol. While budesonide is well absorbed from the GI tract, its oral bioavailability is low (about 10%), primarily because of extensive first-pass metabolism in the liver. Two major metabolites (16α-hydroxyprednisolone and 6β-hydroxybudesonide) are formed via the cytochrome P450 3A enzyme. In vitro studies on the binding of the two primary metabolites to the corticosteroid receptor indicate that their affinity for the receptor is less than 1% of that of the parent compound. It is hoped that use of this drug will avoid the long-term adverse reactions seen with systemically active corticosteroids.

MISCELLANEOUS GI DRUGS

Additional drugs in classes of their own are also used in the treatment and/or prevention of various GI conditions. They include misoprostol, sucralfate, and octreotide.

Misoprostol

Prostaglandins of the A, E, and I type inhibit gastric acid secretion. The prostaglandins also stimulate increased mucus and bicarbonate secretion by gastric mucosa. Misoprostol (*Cytotec*), which is an analogue of prostaglandin E_1, has been approved for use in the prevention of nonsteroidal antiinflammatory drug–induced ulceration. It also is approved in other countries for the treatment of peptic ulcer disease. Misoprostol is absorbed rapidly after oral administration and is hydrolyzed to the active compound. It is metabolized by the liver and excreted mainly in the urine. Adverse effects include crampy abdominal pain, dose-related diarrhea, and uterine contractions. The last-named effect has led to its use in the control of postpartum bleeding (see Chapter 62).

Sucralfate

Sucralfate (*Carafate*) is an aluminum hydroxide–sulfated sucrose complex that is only minimally absorbed from the GI tract. After exposure to gastric acid, the compound becomes negatively charged, creating a viscous adherent complex. This complex is believed to inhibit back-diffusion of H^+. Other effects are a direct reduction in pepsin activity and a slight rise in tissue prostaglandin levels. Stimulation of a cytoprotection mechanism may therefore assist mucosal healing. The drug has no acid-buffering capacity.

Sucralfate is frequently used for prophylaxis of stress-induced gastritis in patients in intensive care units. It has also been successfully used in small numbers of patients as a suspension enema to treat radiation proctitis.

Constipation is the main side effect associated with its oral use. As with other aluminum compounds, the drug may bind phosphorus, resulting in secondary hypophosphatemia. Binding to a number of other coadministered medications may result in a significant reduction in their bioavailability.

Octreotide

Octreotide (*Sandostatin*) is a synthetic somatostatin analogue. It is used in a variety of situations and must be given subcutaneously or intravenously. Most commonly, it is used as a continuous intravenous infusion in patients hospitalized with bleeding varices, because it decreases splanchnic circulation and therefore reduces portal pressures. A long-acting depot form is approved for the suppression of severe diarrhea and flushing associated with malignant carcinoid syndrome and for the treatment of the profuse watery diarrhea associated with vasoactive intestinal peptide tumor.

Study Questions

1. A 36-year-old woman with severe erosive esophagitis is prescribed pantoprazole. One of the most common adverse side effects of such therapy is which of the following?
(A) Vomiting
(B) Constipation
(C) Headache
(D) Heartburn
(E) Paresthesias

2. While taking a NSAID for arthritis, a 65-year-old man developed a gastric ulcer. He was prescribed ranitidine for 8 weeks. This drug binds a receptor located where?
(A) Nucleus
(B) Nucleolus
(C) Cytoplasm
(D) Cell membrane
(E) Cell wall

3. A 20-year-old woman goes to the emergency department, stating that within the past hour she ingested "a handful of sleeping pills." She is still awake. Which of the following drugs can be given to induce vomiting?
(A) Metoclopramide
(B) Ipecac
(C) Morphine
(D) Promethazine
(E) Ondansetron

4. A 17-year-old boy with a history of sulfa allergy is diagnosed with left-side ulcerative colitis after a 3-week history of bloody diarrhea and tenesmus. On examination he is afebrile and has no abdominal tenderness. The appropriate drug therapy to institute initially is which of the following?
(A) Metronidazole
(B) Sulfasalazine
(C) Mesalamine
(D) Cyclosporine
(E) Prednisone

5. A 62-year-old woman on hemodialysis is scheduled for a screening colonoscopy. Which should be prescribed for her colonic preparation?
(A) Visicol
(B) Fleet Phospho soda
(C) Magnesium citrate
(D) Dulcolax
(E) GoLYTELY

6. Gastric acid secretion is stimulated by the presence of
(A) Gastrin and acetylcholine
(B) Histamine and motilin
(C) Norepinephrine and gastrin
(D) Norepinephrine and histamine
(E) Acetylcholine and pepsin

ANSWERS

1. C. The most commonly reported side effects for all of the proton pump inhibitors are headache, diarrhea, and abdominal pain. Heartburn is improved by these agents. Vomiting, constipation, and paresthesias are not typical side effects of proton pump inhibitors.

2. D. Ranitidine is an H_2-receptor antagonist. H_2-receptors are found in the cell membrane of parietal cells, not in the nucleus, nucleolus, or cytoplasm. Mammalian cells do not have cell walls.

3. B. Two medicines, ipecac and apomorphine, induce vomiting. Metoclopramide is a prokinetic with antiemetic properties and therefore would have the opposite of the desired effect. Morphine is an opioid with analgesic and sedating properties. Promethazine and ondansetron are also antiemetics, not emetics.

4. C. The information provided suggests the patient has mild to moderate disease. Initial therapy should be a 5-ASA containing product, which includes sulfasalazine and mesalamine. However, the patient has a sulfa allergy, precluding the use of sulfasalazine. Metronidazole is useful in the treatment of some patients with Crohn's disease. Cyclosporine has been used in patients with fulminant ulcerative colitis. Prednisone may have to be added to this patient's therapy, but only if he fails to respond to the mesalamine. It should not be used initially.

5. **E.** A patient on hemodialysis has end-stage renal disease and therefore cannot tolerate excess magnesium and phosphorus. Visicol and Fleet Phospho soda have phosphates, and magnesium citrate has magnesium. GoLYTELY is an isosmotic unabsorbable electrolyte–polyethylene glycol colonic lavage solution that is safe for patients with end-stage renal disease. Dulcolax is a stimulant cathartic but is not sufficient for colonoscopy preparation.
6. **A.** Gastrin, histamine, and acetylcholine stimulate gastric acid secretion. Pepsin is a digestive protein secreted by the stomach in response to a meal. Norepinephrine is a neurotransmitter that does not affect gastric acid secretion.

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CASE Study Peptic Ulcer Disease

JK is a 32-year-old white woman who works as the administrative assistant to the chief executive officer of a large firm. She has two small children and describes her life as stressful. She smokes 1 pack of cigarettes per day. She frequently takes naproxen for headaches. For the past 5 weeks she has noticed significant epigastric discomfort. This morning she went to the emergency department complaining of hematemesis. She was admitted, and the gastroenterologist performed an upper endoscopy that revealed a 1-cm ulcer. Is further evaluation necessary, and what recommendations would you make to this patient?

ANSWER: Peptic ulcer disease is most frequently secondary to either *Helicobacter pylori* infection or use of NSAIDs. The patient does admit to NSAID use (naproxen), but should also be checked for concomitant *H. pylori* infection at time of endoscopy or by a serology test. If the patient was found to have *H. pylori,* an appropriate eradication regimen should be prescribed. The patient should also be counseled to avoid NSAIDs. The patient should be prescribed a proton pump inhibitor for 8 weeks to heal the ulcer. A repeat endoscopy should be done at that time to document ulcer healing and rule out gastric cancer. In addition, the patient should be counseled to stop smoking, which is a risk factor for more severe peptic ulcer disease.