**LECTURE 3: DRUGS AFFECTING DIGESTION**

**DRUGS USED IN ACID-PEPTIC DISEASES**

Acid-peptic diseases include gastroesophageal reflux, peptic ulcer (gastric and duodenal), and stress-related mucosal injury. In all these conditions, mucosal erosions or ulceration arise when the caustic effects of aggressive factors (acid, pepsin, bile) overwhelm the defensive factors of the gastrointestinal mucosa (mucus and bicarbonate secretion, prostaglandins, blood flow, and the processes of restitution and regeneration after cellular injury). Over 90% of peptic ulcers are caused by infection with the bacterium Helicobacter pylori or by use of nonsteroidal anti-inflammatory drugs (NSAIDs). Drugs used in the treatment of acid-peptic disorders may be divided into two classes: agents that reduce intragastric acidity and agents that promote mucosal defense.

**ANTACIDS**

Antacids have been used for centuries in the treatment of patients with dyspepsia and acid-peptic disorders. They were the mainstay of treatment for acid-peptic disorders until the advent of H2-receptor antagonists and proton-pump inhibitors (PPIs). They continue to be used commonly by patients as nonprescription remedies for the treatment of intermittent heartburn and dyspepsia. Antacids are weak bases that react with gastric hydrochloric acid to form a salt and water. Their principal mechanism of action is reduction of intragastric acidity. After a meal, approximately 45 mEq/h of hydrochloric acid is secreted. A single dose of 156 mEq of antacid given 1 hour after a meal effectively neutralizes gastric acid for up to 2 hours. However, the acid-neutralization capacity among different proprietary formulations of antacids is highly variable, depending on their rate of dissolution (tablet versus liquid), water solubility, rate of reaction with acid, and rate of gastric emptying. Sodium bicarbonate (eg, baking soda) reacts rapidly with hydrochloric acid (HCl) to produce carbon dioxide and sodium chloride. Formation of carbon dioxide results in gastric distention and belching. Unreacted alkali is readily absorbed, potentially causing metabolic alkalosis when given in high doses or to patients with renal insufficiency. Sodium chloride absorption may exacerbate fluid retention in patients with heart failure, hypertension, and renal insufficiency. Calcium carbonate is less soluble and reacts more slowly than sodium bicarbonate with HCl to form carbon dioxide and calcium chloride (CaCl2). Like sodium bicarbonate, calcium carbonate may cause belching or metabolic alkalosis. Calcium carbonate is used for a number of other indications apart from its antacid properties. Excessive doses of either sodium bicarbonate or calcium carbonate with calcium-containing dairy products can lead to hypercalcemia, renal insufficiency, and metabolic alkalosis (milk-alkali syndrome). Formulations containing magnesium hydroxide or aluminum hydroxide react slowly with HCl to form magnesium chloride or aluminum chloride and water. Because no gas is generated, belching does not occur. Metabolic alkalosis is also uncommon because of the efficiency of the neutralization reaction. Because unabsorbed magnesium salts may cause an osmotic diarrhea and aluminum salts may cause constipation, these agents are commonly administered together in proprietary formulations to minimize the impact on bowel function.

Both magnesium and aluminum are absorbed and excreted by the kidneys. Hence, patients with renal insufficiency should not take these agents long-term. All antacids may affect the absorption of other medications by binding the drug (reducing its absorption) or by increasing intragastric pH so that the drug’s dissolution or solubility (especially weakly basic or acidic drugs) is altered. Therefore, antacids should not be given within 2 hours of doses of tetracyclines, fluoroquinolones, itraconazole, and iron.

**H2-RECEPTOR ANTAGONISTS**

H2-receptor antagonists (commonly referred to as H2 blockers) were the most commonly prescribed drugs in the world. With the recognition of the role of *H. pylori* in ulcer disease (which may be treated with appropriate antibacterial therapy) and the advent of PPIs, the use of prescription H2 blockers has declined markedly.

Pharmacodynamics

The H2 antagonists exhibit competitive inhibition at the parietal cell H2 receptor and suppress basal and meal-stimulated acid secretion in a linear, dose-dependent manner. They are highly selective and do not affect H1 or H3 receptors. The volume of gastric secretion and the concentration of pepsin are also reduced. H2 antagonists reduce acid secretion stimulated by histamine as well as by gastrin and cholinomimetic agents through two mechanisms. First, histamine released from ECL cells by gastrin or vagal stimulation is blocked from binding to the parietal cell H2 receptor. Second, direct stimulation of the parietal cell by gastrin or acetylcholine has a diminished effect on acid secretion in the presence of H2-receptor blockade. The potencies of the four H2-receptor antagonists vary over a 50-fold range. When given in usual prescription doses, however, all inhibit 60–70% of total 24-hour acid secretion. H2 antagonists are especially effective at inhibiting nocturnal acid secretion (which depends largely on histamine), but they have a modest impact on meal-stimulated acid secretion (which is stimulated by gastrin and acetylcholine as well as histamine). Therefore, nocturnal and fasting intragastric pH is raised to 4–5, but the impact on the daytime, meal-stimulated pH profile is less. Recommended prescription doses maintain greater than 50% acid inhibition for 10 hours; hence, these drugs are commonly given twice daily. At doses available in over-the-counter formulations, the duration of acid inhibition is 6–10 hours.

Clinical Uses H2-receptor antagonists continue to be prescribed, but PPIs (see below) are more commonly prescribed than H2 antagonists for most clinical indications. The over-the-counter preparations of the H2 antagonists are heavily used by the public.

**1. Gastroesophageal reflux disease (GERD)**—Patients with infrequent heartburn or dyspepsia (fewer than three times per week) may take either antacids or intermittent H2 antagonists. Because antacids provide rapid acid neutralization, they afford faster symptom relief than H2 antagonists. However, the effect of antacids is short-lived (1–2 hours) compared with H2 antagonists (6–10 hours). H2 antagonists may be taken prophylactically before meals in an effort to reduce the likelihood of heartburn. Frequent heartburn is better treated with twice-daily H2 antagonists or PPIs. In patients with erosive esophagitis (approximately 50% of patients with GERD), H2 antagonists afford healing in less than 50% of patients; hence PPIs are preferred because of their superior acid inhibition.

**2. Peptic ulcer disease**—PPIs have largely replaced H2 antagonists in the treatment of acute peptic ulcer disease. Nevertheless, H2 antagonists are still sometimes used. Nocturnal acid suppression by H2 antagonists affords effective ulcer healing in most patients with uncomplicated gastric and duodenal ulcers. Hence, all the agents may be administered once daily at bedtime, resulting in ulcer healing rates >80–90% after 6–8 weeks of therapy.

For patients with ulcers caused by aspirin or other NSAIDs, the NSAID should be discontinued. If the NSAID must be continued for clinical reasons despite active ulceration, a PPI should be given instead of an H2 antagonist to more reliably promote ulcer healing. For patients with acute peptic ulcers caused by H pylori, H2 antagonists no longer play a significant therapeutic role. H pylori should be treated with a 10- to 14-day course of therapy including a PPI and two or three antibiotics (see below).

**3. Nonulcer dyspepsia**—H2 antagonists are commonly used as over-the-counter agents and prescription agents for treatment of intermittent dyspepsia not caused by peptic ulcer. However, benefit compared with placebo has never been convincingly demonstrated.

**4. Prevention of bleeding from stress-related gastritis**— Clinically important bleeding from upper gastrointestinal erosions or ulcers occurs in 1–5% of critically ill patients as a result of impaired mucosal defense mechanisms caused by poor perfusion. Although most critically ill patients have normal or decreased acid secretion, numerous studies have shown that agents that increase intragastric pH (H2 antagonists or PPIs) reduce the incidence of clinically significant bleeding and should be administered to patients who are at high risk of gastrointestinal bleeding. However, the optimal agent is uncertain. For patients who are unable to receive enteral medications, either intravenous H2 antagonists or PPIs may be administered. Continuous infusions of H2 antagonists are generally preferred to bolus infusions because they achieve more consistent, sustained elevation of intragastric pH. Adverse Effects H2 antagonists are extremely safe drugs. Adverse effects occur in less than 3% of patients and include diarrhea, headache, fatigue, myalgias, and constipation. Some studies suggest that intravenous H2 antagonists (or PPIs) may increase the risk of nosocomial pneumonia in critically ill patients. Mental status changes (confusion, hallucinations, agitation) may occur with administration of intravenous H2 antagonists, especially in patients in the intensive care unit who are elderly or who have renal or hepatic dysfunction. These events may be more common with cimetidine. Mental status changes rarely occur in ambulatory patients. Cimetidine inhibits binding of dihydrotestosterone to androgen receptors, inhibits metabolism of estradiol, and increases serum prolactin levels. When used long-term or in high doses, it may cause gynecomastia or impotence in men and galactorrhea in women. These effects are specific to cimetidine and do not occur with the other H2 antagonists. Although there are no known harmful effects on the fetus, H2 antagonists cross the placenta. Therefore, they should not be administered to pregnant women unless absolutely necessary. The H2 antagonists are secreted into breast milk and may therefore affect nursing infants. H2 antagonists may rarely cause blood dyscrasias. Blockade of cardiac H2 receptors may cause bradycardia, but this is rarely of clinical significance. Rapid intravenous infusion may cause bradycardia and hypotension through blockade of cardiac H2 receptors; therefore, intravenous infusions should be given over 30 minutes. H2 antagonists rarely cause reversible abnormalities in liver chemistry.

**PROTON-PUMP INHIBITORS (PPIs)**

Since their introduction in the late 1980s, these efficacious acid inhibitory agents have assumed the major role for the treatment of acid-peptic disorders. PPIs are now among the most widely prescribed drugs worldwide.

Six PPIs are available for clinical use: omeprazole, esomeprazole, lansoprazole, dexlansoprazole, rabeprazole, and pantoprazole. All are substituted benzimidazoles that resemble H2 antagonists in structure but have a completely different mechanism of action. Omeprazole and lansoprazole are racemic mixtures of R- and S-isomers. Esomeprazole is the S-isomer of omeprazole and dexlansoprazole the R-isomer of lansoprazole. All are available in oral formulations. Esomeprazole and pantoprazole are also available in intravenous formulations.

PPIs are administered as inactive prodrugs. To protect the acidlabile prodrug from rapid destruction within the gastric lumen, oral products are formulated for delayed release as acid-resistant, enteric-coated capsules or tablets. After passing through the stomach into the alkaline intestinal lumen, the enteric coatings dissolve and the prodrug is absorbed. For children or patients with dysphagia or enteral feeding tubes, capsule formulations (but not tablets) may be opened and the microgranules mixed with apple or orange juice or mixed with soft foods (eg, applesauce). Esomeprazole, omeprazole, and pantoprazole are also available as oral suspensions. Lansoprazole is available as a tablet formulation that disintegrates in the mouth, and rabeprazole is available in a formulation that may be sprinkled on food. Omeprazole is also available as a powder formulation (capsule or packet) that contains sodium bicarbonate to protect the naked (non-enteric-coated) drug from acid degradation. When administered on an empty stomach by mouth or enteral tube, this “immediate-release” suspension results in rapid omeprazole absorption and onset of acid inhibition.

**Clinical Uses**

**1. Gastroesophageal reflux disease**—PPIs are the most effective agents for the treatment of erosive reflux disease, esophageal complications of reflux disease (peptic stricture or Barrett’s esophagus), and extraesophageal manifestations of reflux disease. Once-daily dosing provides effective symptom relief and tissue healing in 85–90% of patients; up to 15% of patients require twice-daily dosing. GERD symptoms recur in over 80% of patients within 6 months after discontinuation of a PPI. For patients with erosive esophagitis or esophageal complications, long-term daily maintenance therapy with a full-dose or half-dose PPI is usually needed. Many patients with nonerosive GERD may be treated successfully with intermittent courses of PPIs or H2 antagonists taken as needed (“on demand”) for recurrent symptoms.

In current clinical practice, many patients with symptomatic GERD are treated empirically with medications without prior endoscopy, ie, without knowledge of whether the patient has erosive or nonerosive reflux disease. Empiric treatment with PPIs provides sustained symptomatic relief in 70–80% of patients, compared with 50–60% with H2 antagonists. Because of recent cost reductions, PPIs are used increasingly as first-line therapy for patients with symptomatic GERD. Due to recent safety concerns, however, initial empiric treatment with an H2 antagonist should be considered. Sustained acid suppression with twice-daily PPIs for at least 3 months is used to treat extraesophageal complications of reflux disease (asthma, chronic cough, laryngitis, and noncardiac chest pain).

**2. Peptic ulcer disease**—Compared with H2 antagonists, PPIs afford more rapid symptom relief and faster ulcer healing for duodenal ulcers and, to a lesser extent, gastric ulcers. All the pump inhibitors heal more than 90% of duodenal ulcers within 4 weeks and a similar percentage of gastric ulcers within 6–8 weeks.

**a. H pylori-associated ulcers**—For H pylori-associated ulcers, there are two therapeutic goals: to heal the ulcer and to eradicate the organism. The most effective regimens for H pylori eradication are combinations of two antibiotics and a PPI. PPIs promote eradication of H pylori through several mechanisms: direct antimicrobial properties (minor) and—by raising intragastric pH-lowering the minimal inhibitory concentrations of antibiotics against H pylori. Until recently, the most commonly recommended treatment regimen consisted of a 14-day regimen of “triple therapy”: a PPI twice daily; clarithromycin, 500 mg twice daily; and either amoxicillin, 1 g twice daily, or metronidazole, 500 mg twice daily. Due to increasing treatment failures attributable to rising clarithromycin resistance, “quadruple therapy” is now recommended as first-line treatment for patients who likely have clarithromycin resistance due to prior exposure or to residence in regions with high clarithromycin resistance. Two 14-day treatment regimens currently are recommended. Each includes a PPI twice daily with either: (a) bismuth subsalicylate 524 mg, metronidazole 500 mg, and tetracycline 500 mg, all given four times daily; or (b) amoxicillin 1 g, clarithromycin 500 mg, and metronidazole 500 mg, all given twice daily. After completion of antibiotic therapy, the PPI should be continued once daily for a total of 4–6 weeks to ensure complete ulcer healing.

**b. NSAID-associated ulcers**—For patients with ulcers caused by aspirin or other NSAIDs, either H2 antagonists or PPIs provide rapid ulcer healing so long as the NSAID is discontinued; however, continued use of the NSAID impairs ulcer healing. In patients with NSAID-induced ulcers who require continued NSAID therapy, treatment with a PPI more reliably promotes ulcer healing. Asymptomatic peptic ulceration develops in 10–20% of people taking frequent NSAIDs, and ulcer-related complications (bleeding, perforation) develop in 1–2% of persons per year. PPIs taken once daily are effective in reducing the incidence of ulcers and ulcer complications in patients taking aspirin or other NSAIDs.

**c. Prevention of rebleeding from peptic ulcers**—In patients with acute gastrointestinal bleeding due to peptic ulcers, the risk of rebleeding from ulcers that have a visible vessel or adherent clot is increased. Rebleeding of this subset of high-risk ulcers is reduced significantly with PPIs administered for 3–5 days either as high-dose oral therapy (eg, omeprazole, 40 mg orally twice daily) or as a continuous intravenous infusion. It is believed that an intragastric pH higher than 6 may enhance coagulation and platelet aggregation. The optimal dose of intravenous PPI needed to achieve and maintain this level of near-complete acid inhibition is unknown; however, initial bolus administration of esomeprazole or pantoprazole (80 mg) followed by constant infusion (8 mg/h) is commonly recommended.

**3. Nonulcer dyspepsia**—PPIs have modest efficacy for treatment of nonulcer dyspepsia, benefiting 10–20% more patients than placebo. Despite their use for this indication, superiority to H2 antagonists (or even placebo) has not been conclusively demonstrated.

**4. Prevention of stress-related mucosal bleeding**—As discussed previously (see H2-Receptor Antagonists), PPIs (given orally, by nasogastric tube, or by intravenous infusions) may be administered to reduce the risk of clinically significant stressrelated mucosal bleeding in critically ill patients. The only PPI approved by the US Food and Drug Administration (FDA) for this indication is an oral immediate-release omeprazole formulation, which is administered by nasogastric tube twice daily on the first day, then once daily. Although not FDA approved for this indication, other PPI suspension formulations (esomeprazole, omeprazole, pantoprazole) may also be used. For patients with nasoenteric tubes, PPI suspensions may be preferred to intravenous H2 antagonists or PPIs because of comparable efficacy, lower cost, and ease of administration. For patients without a nasoenteric tube or with significant ileus, intravenous H2 antagonists are preferred to intravenous PPIs because of their proven efficacy. Although PPIs are increasingly used, there are no controlled trials demonstrating efficacy or optimal dosing.

**5. Gastrinoma and other hypersecretory conditions**— Patients with isolated gastrinomas are best treated with surgical resection. In patients with metastatic or unresectable gastrinomas, massive acid hypersecretion results in peptic ulceration, erosive esophagitis, and malabsorption. With PPIs, excellent acid suppression can be achieved in all patients. Dosage is titrated to reduce basal acid output to less than 5–10 mEq/h. Typical doses of omeprazole are 60–120 mg/d.

**Adverse Effects**

**1. General**—Although PPIs have been considered to be extremely safe, a number of recent safety concerns have been raised. As with most drugs, PPIs should be prescribed at the lowest effective dose and the risks versus benefits of long-term use carefully weighed. Diarrhea, headache, and abdominal pain are reported in 1–5% of patients, although the frequency of these events is only slightly increased compared with placebo. In large observational studies, PPIs have been associated with an increased risk of acute interstitial nephritis and chronic kidney disease compared to nonusers or users of H2-receptor antagonists. A mechanism by which kidney damage might occur has not been determined. Some epidemiologic studies have also detected an increased risk of dementia in long-term PPI users, although causality has not been established. PPIs are not teratogenic in animal models; however, safety during pregnancy has not been established.

**2. Nutrition**—Acid is important in releasing vitamin B12 from food. A minor reduction in oral cyanocobalamin absorption occurs during proton-pump inhibition, potentially leading to subnormal B12 levels with prolonged therapy. Acid also promotes absorption of food-bound minerals (non-heme iron, insoluble calcium salts, magnesium). Meta-analyses of cohort and case-control studies have detected a modest increase in the risk of hip fracture in patients taking long-term PPIs. Although a causal relationship is unproven, PPIs may reduce calcium absorption or inhibit osteoclast function. All PPIs carry an FDA-mandated warning of a possible increased risk of hip, spine, and wrist fractures. Patients who require long-term PPIs—especially those with risk factors for osteoporosis—should have monitoring of bone density and should be provided calcium supplements. Cases of severe, lifethreatening hypomagnesemia with secondary hypocalcemia due to PPIs have been reported, possibly due to decreased intestinal absorption.

**3. Respiratory and enteric infections**—Gastric acid is an important barrier to colonization and infection of the stomach and intestine from ingested bacteria. Increases in gastric bacterial concentrations are detected in patients taking PPIs, which is of unknown clinical significance. Some studies have reported an increased risk of both community-acquired respiratory infections and nosocomial pneumonia among patients taking PPIs. There is a two- to threefold increased risk for hospital- and community-acquired Clostridium difficile infection in patients taking PPIs. There also is a small increased risk of other enteric infections (eg, Salmonella, Shigella, Escherichia coli, Campylobacter), which should be considered particularly when traveling in underdeveloped countries.

**4. Potential problems due to increased serum gastrin**— Gastrin levels are regulated by intragastric acidity. Acid suppression alters normal feedback inhibition so that median serum gastrin levels rise 1.5- to twofold in patients taking PPIs. Although gastrin levels remain within normal limits in most patients, they exceed 500 pg/mL (normal, long time also may exhibit ECL hyperplasia, carcinoid tumor formation has not been documented. At present, routine monitoring of serum gastrin levels is not recommended in patients receiving prolonged PPI therapy.

**5. Other potential problems due to decreased gastric acidity**—Among patients infected with H pylori, long-term acid suppression leads to increased chronic inflammation in the gastric body and decreased inflammation in the antrum. Concerns have been raised that increased gastric inflammation may accelerate gastric gland atrophy (atrophic gastritis) and intestinal metaplasia—known risk factors for gastric adenocarcinoma. A special FDA Gastrointestinal Advisory Committee concluded that there is no evidence that prolonged PPI therapy produces the kind of atrophic gastritis (multifocal atrophic gastritis) or intestinal metaplasia that is associated with increased risk of adenocarcinoma. Routine testing for H pylori is not recommended in patients who require long-term PPI therapy. Longterm PPI therapy is associated with the development of small benign gastric fundic-gland polyps in a small number of patients, which may disappear after stopping the drug and are of uncertain clinical significance.

**MUCOSAL PROTECTIVE AGENTS**

The gastroduodenal mucosa has evolved a number of defense mechanisms to protect itself against the noxious effects of acid and pepsin. Both mucus and epithelial cell-cell tight junctions restrict back diffusion of acid and pepsin. Epithelial bicarbonate secretion establishes a pH gradient within the mucous layer in which the pH ranges from 7 at the mucosal surface to 1–2 in the gastric lumen. Blood flow carries bicarbonate and vital nutrients to surface cells. Areas of injured epithelium are quickly repaired by restitution, a process in which migration of cells from gland neck cells seals small erosions to reestablish intact epithelium. Mucosal prostaglandins appear to be important in stimulating mucus and bicarbonate secretion and mucosal blood flow. A number of agents that potentiate these mucosal defense mechanisms are available for the prevention and treatment of acid-peptic disorders.

**SUCRALFATE**

**Chemistry & Pharmacokinetics**

Sucralfate is a salt of sucrose complexed to sulfated aluminum hydroxide. In water or acidic solutions it forms a viscous, tenacious paste that binds selectively to ulcers or erosions for up to 6 hours. Sucralfate has limited solubility, breaking down into sucrose sulfate (strongly negatively charged) and an aluminum salt. Less than 3% of intact drug and aluminum is absorbed from the intestinal tract; the remainder is excreted in the feces.

**Pharmacodynamics**

A variety of beneficial effects have been attributed to sucralfate, but the precise mechanism of action is unclear. It is believed that the negatively charged sucrose sulfate binds to positively charged proteins in the base of ulcers or erosion, forming a physical barrier that restricts further caustic damage and stimulates mucosal prostaglandin and bicarbonate secretion.

**Clinical Uses**

Sucralfate is administered in a dosage of 1 g four times daily on an empty stomach (at least 1 hour before meals). At present, its clinical uses are limited. Sucralfate (administered as a slurry through a nasogastric tube) reduces the incidence of clinically significant upper gastrointestinal bleeding in critically ill patients hospitalized in the intensive care unit, although it is slightly less effective than intravenous H2 antagonists. Sucralfate is still used by many clinicians for prevention of stress-related bleeding because of concerns that acid inhibitory therapies (antacids, H2 antagonists, and PPIs) may increase the risk of nosocomial pneumonia.

**Adverse Effects**

Because it is not absorbed, sucralfate is virtually devoid of systemic adverse effects. Constipation occurs in 2% of patients due to the aluminum salt. Because a small amount of aluminum is absorbed, it should not be used for prolonged periods in patients with renal insufficiency.

**PROSTAGLANDIN ANALOGS**

**Chemistry & Pharmacokinetics**

The human gastrointestinal mucosa synthesizes a number of prostaglandins; the primary ones are prostaglandins E and F. Misoprostol, a methyl analog of PGE1, has been approved for gastrointestinal conditions. After oral administration, it is rapidly absorbed and metabolized to a metabolically active free acid. The serum half-life is less than 30 minutes; hence, it must be administered 3–4 times daily. It is excreted in the urine; however, dose reduction is not needed in patients with renal insufficiency. Misoprostol has both acid inhibitory and mucosal protective properties. It is believed to stimulate mucus and bicarbonate secretion and enhance mucosal blood flow. Misoprostol can reduce the incidence of NSAID-induced ulcers to less than 3% and the incidence of ulcer complications by 50%. It is approved for prevention of NSAID-induced ulcers in high-risk patients; however, misoprostol has never achieved widespread use owing to its high adverse-effect profile and need for multiple daily dosing.

**BISMUTH COMPOUNDS**

**Chemistry & Pharmacokinetics**

Two bismuth compounds are available: bismuth subsalicylate, a nonprescription formulation containing bismuth and salicylate, and bismuth subcitrate potassium. In the USA, bismuth subcitrate is available only as a combination prescription product that also contains metronidazole and tetracycline for the treatment of H pylori. Bismuth subsalicylate undergoes rapid dissociation within the stomach, allowing absorption of salicylate. Over 99% of the bismuth appears in the stool.

**Pharmacodynamics**

The precise mechanisms of action of bismuth are unknown. Bismuth coats ulcers and erosions, creating a protective layer against acid and pepsin. It may also stimulate prostaglandin, mucus, and bicarbonate secretion. Bismuth subsalicylate reduces stool frequency and liquidity in acute infectious diarrhea, due to salicylate inhibition of intestinal prostaglandin and chloride secretion. Bismuth has direct antimicrobial effects and binds enterotoxins, accounting for its benefit in preventing and treating traveler’s diarrhea. Bismuth compounds have direct antimicrobial activity against H pylori.

**Adverse Effects**

All bismuth formulations have excellent safety profiles. Bismuth causes harmless blackening of the stool, which may be confused with gastrointestinal bleeding. Liquid formulations may cause harmless darkening of the tongue. Bismuth agents should be used for short periods only and should be avoided in patients with renal insufficiency. Prolonged usage of some bismuth compounds may rarely lead to bismuth toxicity, resulting in encephalopathy (ataxia, headaches, confusion, seizures). However, such toxicity is not reported with bismuth subsalicylate or bismuth citrate. High dosages of bismuth subsalicylate may lead to salicylate toxicity.

**DRUGS STIMULATING GASTROINTESTINAL MOTILITY**

Drugs that can selectively stimulate gut motor function (prokinetic agents) have significant potential clinical usefulness. Agents that increase lower esophageal sphincter pressures may be useful for GERD. Drugs that improve gastric emptying may be helpful for gastroparesis and postsurgical gastric emptying delay. Agents that stimulate the small intestine may be beneficial for postoperative ileus or chronic intestinal pseudoobstruction. Finally, agents that enhance colonic transit may be useful in the treatment of constipation. Unfortunately, only a limited number of agents in this group are available for clinical use at this time.

**CHOLINOMIMETIC AGENTS**

Cholinomimetic agonists such as bethanechol stimulate muscarinic M3 receptors on muscle cells and at myenteric plexus synapses. Bethanechol was used in the past for the treatment of GERD and gastroparesis. Owing to multiple cholinergic effects and the advent of less toxic agents, it is now seldom used. The acetylcholinesterase inhibitor neostigmine can enhance gastric, small intestine, and colonic emptying. Intravenous neostigmine is used for the treatment of hospitalized patients with acute large bowel distention (known as acute colonic pseudo-obstruction or Ogilvie’s syndrome). Administration of 2 mg results in prompt colonic evacuation of flatus and feces in the majority of patients. Cholinergic effects include excessive salivation, nausea, vomiting, diarrhea, and bradycardia.

**METOCLOPRAMIDE & DOMPERIDONE**

Metoclopramide and domperidone are dopamine D2-receptor antagonists. Within the gastrointestinal tract, activation of dopamine receptors inhibits cholinergic smooth muscle stimulation; blockade of this effect is believed to be the primary prokinetic mechanism of action of these agents. These agents increase esophageal peristaltic amplitude, increase lower esophageal sphincter pressure, and enhance gastric emptying but have no effect on small intestine or colonic motility. Metoclopramide and domperidone also block dopamine D2 receptors in the chemoreceptor trigger zone of the medulla (area postrema), resulting in potent antinausea and antiemetic action.

**MACROLIDES**

Macrolide antibiotics such as erythromycin directly stimulate motilin receptors on gastrointestinal smooth muscle and promote the onset of a migrating motor complex. Intravenous erythromycin (3 mg/kg) is beneficial in some patients with gastroparesis; however, tolerance rapidly develops. It may be used in patients with acute upper gastrointestinal hemorrhage to promote gastric emptying of blood before endoscopy.

**LAXATIVES**

The overwhelming majority of people do not need laxatives; yet they are self-prescribed by a large portion of the population. For most people, intermittent constipation is best prevented with a high-fiber diet, adequate fluid intake, regular exercise, and the heeding of nature’s call. Patients not responding to dietary changes or fiber supplements should undergo medical evaluation before initiating long-term laxative treatment. Laxatives may be classified by their major mechanism of action, but many work through more than one mechanism.

**BULK-FORMING LAXATIVES**

Bulk-forming laxatives are indigestible, hydrophilic colloids that absorb water, forming a bulky, emollient gel that distends the colon and promotes peristalsis. Common preparations include natural plant products (psyllium, methylcellulose) and synthetic fibers (polycarbophil). Bacterial digestion of plant fibers within the colon may lead to increased bloating and flatus.

**STOOL SURFACTANT AGENTS (SOFTENERS)**

These agents soften stool material, permitting water and lipids to penetrate. They may be administered orally or rectally. Common agents include docusate (oral or enema) and glycerin suppository. In hospitalized patients, docusate is commonly prescribed to prevent constipation and minimize straining. Mineral oil is a clear, viscous oil that lubricates fecal material, retarding water absorption from the stool. It is used to prevent and treat fecal impaction in young children and debilitated adults. It is not palatable but may be mixed with juices. Aspiration can result in a severe lipid pneumonitis. Long-term use can impair absorption of fat-soluble vitamins (A, D, E, K).

**OSMOTIC LAXATIVES**

The colon can neither concentrate nor dilute fecal fluid: fecal water is isotonic throughout the colon. Osmotic laxatives are soluble but nonabsorbable compounds that result in increased stool liquidity due to an obligate increase in fecal fluid.

**Nonabsorbable Sugars or Salts**

These agents may be used for the treatment of acute constipation or the prevention of chronic constipation. Magnesium hydroxide (milk of magnesia) is a commonly used osmotic laxative. It should not be used for prolonged periods in patients with renal insufficiency due to the risk of hypermagnesemia. Sorbitol and lactulose are nonabsorbable sugars that can be used to prevent or treat chronic constipation. These sugars are metabolized by colonic bacteria, producing severe flatus and cramps. High doses of osmotically active agents produce prompt bowel evacuation (purgation) within 1–3 hours. The rapid movement of water into the distal small bowel and colon leads to a high volume of liquid stool followed by bowel evacuation. Several purgatives are available, which may be used for the treatment of acute constipation or to cleanse the bowel prior to medical procedures (eg, colonoscopy). These include magnesium citrate, sulfate solution, and a proprietary combination of magnesium oxide, sodium picosulfate, and citrate. When taking these purgatives, it is very important that patients maintain adequate hydration by taking increased oral liquids to compensate for fecal fluid loss. Sodium phosphate also is available—by prescription—as a tablet formulation but is infrequently used due to the risk of hyperphosphatemia, hypocalcemia, hypernatremia, and hypokalemia. Although these electrolyte abnormalities are clinically insignificant in most patients, they may lead to cardiac arrhythmias or acute renal failure due to tubular deposition of calcium phosphate (nephrocalcinosis). Sodium phosphate preparations should not be used in patients who are frail or elderly, have renal insufficiency, have significant cardiac disease, or are unable to maintain adequate hydration during bowel preparation.

**Balanced Polyethylene Glycol**

Lavage solutions containing polyethylene glycol (PEG) are commonly used for complete colonic cleansing before gastrointestinal endoscopic procedures. These balanced, isotonic solutions contain an inert, nonabsorbable, osmotically active sugar (PEG) with sodium sulfate, sodium chloride, sodium bicarbonate, and potassium chloride. The solution is designed so that no significant intravascular fluid or electrolyte shifts occur. Therefore, they are safe for all patients. For optimal bowel cleansing, 1–2 L of solution should be ingested rapidly (over 1–2 hours) on the evening before the procedure and again 4–6 hours before the procedure. For treatment or prevention of chronic constipation, smaller doses of PEG powder may be mixed with water or juices (17 g/8 oz) and ingested daily. In contrast to sorbitol or lactulose, PEG does not produce significant cramps or flatus.