DRUGS USED IN ACID-PEPTIC DISEASES

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Reference: Basic & Clinical Pharmacology: Bertrum G. Katzung and Anthony J. Treveror, 13th edition, 2015, chapter 62, p.1052-1061

Learning Objectives:

At the end of session, the student should be able to:

1. Classify drugs used in acid-peptic diseases.
2. List drugs belonging to each classes.
3. Explain pharmacodynamics of H2-receptor antagonists.
4. State clinical uses of H2-receptor antagonists.
5. Describe side effects of H2-receptor anatgonists.
6. Explain pharmacodynamics of proton pump inhibitors.
7. Explain pharmacokinetics of proton pump inhibitors.
8. State clinical uses of proton pump inhibitors.
9. Describe side effects of proton pump inhibitors.
10. Explain pharmacodynamics, uses and side effects of cytoprotectives.
11. State regimen for eradication of H. pylori.
12. Explain pharmacodynamics, uses and side effects of antacids.

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).

Drug Therapy

Drugs used in the treatment of acid-peptic disorders may be divided into following classes:

- Antisecretory drugs to block gastric acid secretion
- Cytoprotectives to increase mucosal defense
- Antibiotics to eradication H. pylori
- Antacids to neutralize excess gastric acid

Agents that block gastric acid secretion

Three important physiological factors that stimulate gastric acid secretion are histamine, acetylcholine and gastrin. The parietal cell contains receptors for gastrin (CCK-B), histamine (H2), and acetylcholine (muscarinic, M3) (Figure1). When acetylcholine (from vagal postganglionic nerves) or gastrin (released from antral G cells into the blood) bind to the parietal cell receptors, they cause an increase in cytosolic calcium, which in turn stimulates protein kinases that stimulate acid secretion from a H+/K+-ATPase (the proton pump) on the canalicular surface. In close proximity to the parietal cells are gut endocrine cells called **enterochromaffin-like (ECL) cells**. ECL cells also have receptors for gastrin and acetylcholine, which stimulate histamine release. Histamine binds to the H2 receptor on the parietal cell, resulting in activation of adenylyl cyclase, which increases intracellular cyclic

adenosine monophosphate (cAMP) and activates protein kinases that stimulate acid secretion by the H+/K+-ATPase. In humans, it is believed that the major effect of gastrin upon acid secretion is mediated indirectly through the release of histamine from ECL cells rather than through direct parietal cell stimulation. In contrast, acetylcholine provides potent direct parietal cell stimulation.

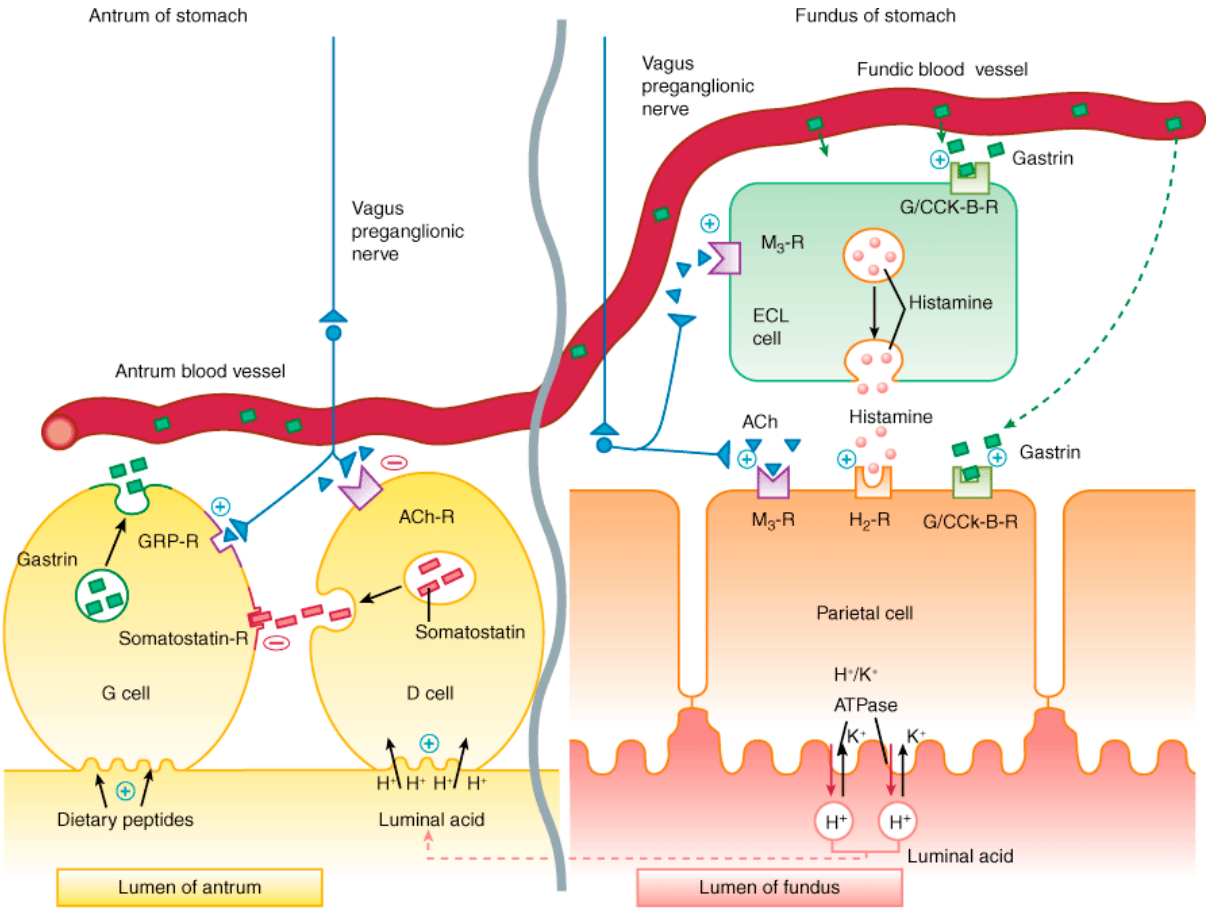

Figure 1: Schematic model for physiologic control of hydrogen ion (acid) secretion by the parietal cells of the gastric fundic glands

H2-Receptor Antagonists

Until the early 1990s, 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

H2 antagonists are in clinical use in Iran: **cimetidine, ranitidine, and famotidine**. The H2 antagonists exhibit competitive inhibition at the parietal cell H2 receptor and suppress basal and meal-stimulated acid secretion (Figure 2) in a linear, dose-dependent manner. 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 H2-receptor antagonists vary with cimetidine being the least and famotidine the most potent H2 blocker. When given in usual prescription doses however, all inhibit 60–70% of total 24-hour acid secretion (have same efficacy). 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).

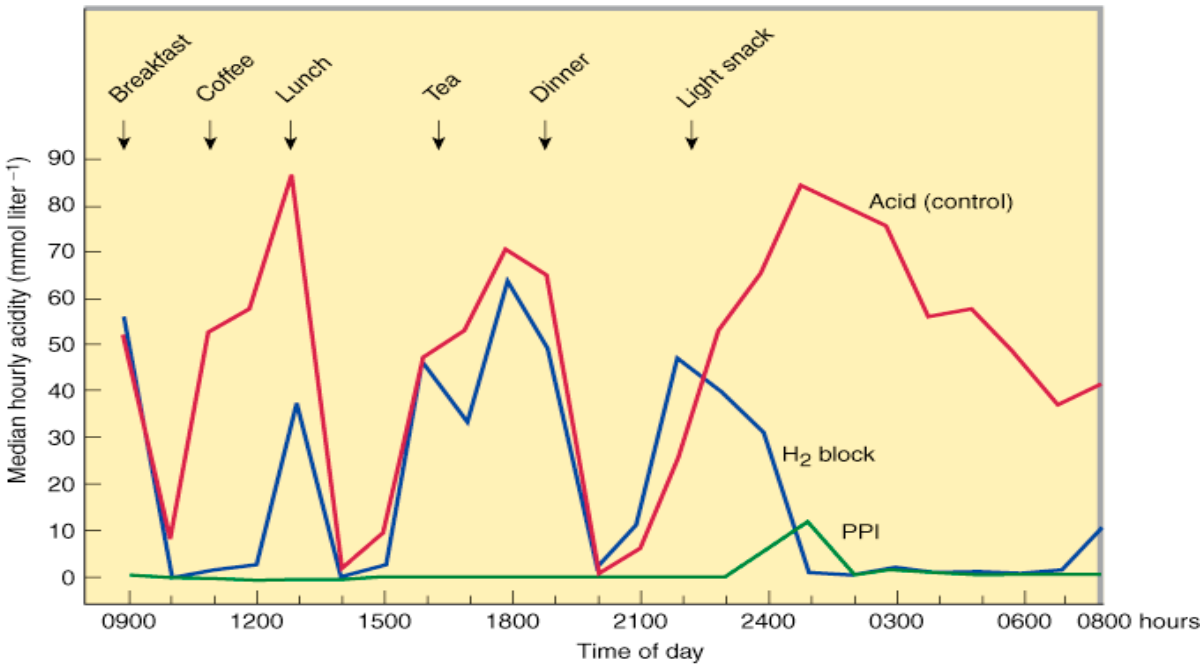

Figure 2: Twenty-four-hour median intragastric acidity pretreatment (red) and after 1 month of treatment with either ranitidine, 150 mg twice daily (blue, H2 block), or omeprazole, 20 mg once daily (green, PPI).

Clinical Uses

H2-receptor antagonists continue to be prescribed but PPIs are steadily replacing H2 antagonists for most clinical indications. However, 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 3 times per week) may take intermittent H2 antagonists. 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, H2 antagonists afford healing in less than 50% of patients; hence PPIs are preferred because of their superior acid inhibition.

2. Peptic ulcer disease: H2 antagonists are still sometimes used in the treatment of acute peptic ulcer disease. Nocturnal acid suppression by H2 antagonists affords effective ulcer healing in most patients with uncomplicated gastric and duodenal ulcers. For healing of NSAID-induced peptic ulcer, 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.

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. Increase intragastric pH by H2 antagonists reduce the incidence of clinically significant bleeding. For patients without a nasoenteric tube or with significant ileus, intravenous H2 antagonists are preferable over

intravenous PPIs because of their proven efficacy and lower cost. Continuous infusions of H2 antagonists are generally preferred to bolus infusions because they achieve more consistent, sustained elevation of intragastric pH.

Adverse Effects

Generally, H2 antagonists are extremely safe drugs.

Effect on central nervous system: 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.

Endocrine effect: 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.

Proton-Pump Inhibitors (PPIs)

PPIs are now among the most widely prescribed drugs worldwide due to their outstanding efficacy and safety.

Six PPIs are available for clinical use: **omeprazole, esomeprazole, lansoprazole, dexlansoprazole, rabeprazole, a**nd **pantoprazole.**

Pharmacokinetics

PPIs are administered as inactive prodrugs. To protect the acid labile 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. The PPIs are lipophilic weak bases (pKa 4–5) and after intestinal absorption diffuse readily across lipid

membranes into acidified compartments (eg, the parietal cell canaliculus). The prodrug rapidly becomes protonated within the canaliculus and rapidly undergoes a molecular conversion to the active form, a reactive thiophilic sulfenamide cation (Figure3), which forms a covalent disulfide bond with the H+/K+-ATPase, irreversibly inactivating the enzyme.

The bioavailability of all agents is decreased approximately 50% by food; hence, the drugs should be administered on an empty stomach. In a fasting state, only 10% of proton pumps are actively secreting acid and susceptible to inhibition. PPIs should be administered approximately 1 hour before a meal (usually breakfast), so that the peak serum concentration coincides with the maximal activity of proton-pump secretion. The drugs have a short serum half-life of about 1.5 hours, but acid inhibition lasts up to 24 hours owing to the irreversible inactivation of the proton pump. At least 18 hours are required for synthesis of new H+/K+-ATPase pump molecules.

Because not all proton pumps are inactivated with the first dose of medication, up to 3–4 days of daily medication are required before the full acid-inhibiting potential is reached. Similarly, after stopping the drug, it takes 3–4 days for full acid secretion to return.

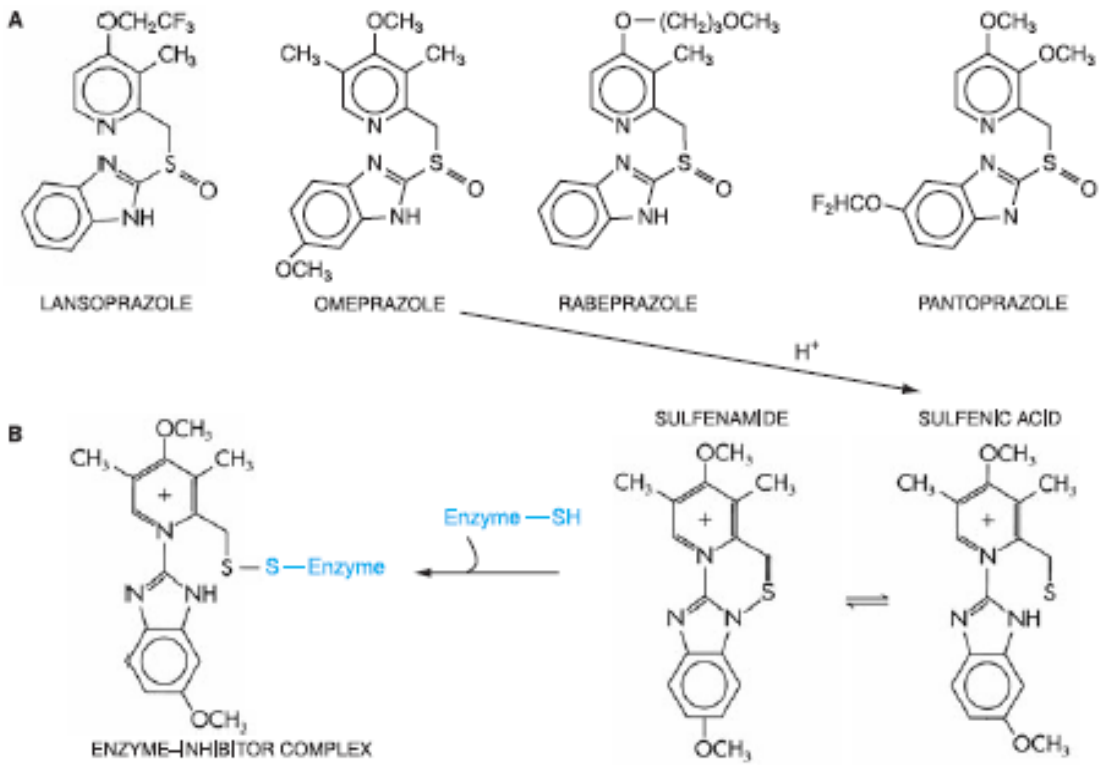

Figure 3: Molecular structures of PPIs and conversion of omeprazole to active form

Pharmacodynamics

In contrast to H2 antagonists, PPIs inhibit both fasting and meal stimulated secretion because they block the final common pathway of acid secretion, the proton pump. In standard doses, PPIs inhibit 90–98% of 24-hour acid secretion (2). When administered at equivalent doses, the different agents show little difference in clinical efficacy.

Clinical Uses

1. Gastroesophageal reflux disease: PPIs are the most effective agents for the treatment of nonerosive and erosive reflux disease, esophageal complications of reflux disease (peptic stricture or Barrett's esophagus), and extraesophageal manifestations of reflux disease (asthma, chronic cough, laryngitis, and noncardiac chest pain).

PPIs are used increasingly as first-line therapy for patients with symptomatic GERD.

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. PPIs are used for treating **H pylori-associated ulcers and NSAID-associated ulcers.** They also are used for **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. It is believed that an intragastric pH higher than 6 may enhance coagulation and platelet aggregation.

3. Nonulcer dyspepsia*:* PPIs have modest efficacy for treatment of nonulcer dyspepsia. 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*:* PPIs (given orally, by nasogastric tube, or by intravenous infusions) may be administered to reduce the risk of clinically significant stress-related mucosal bleeding in critically ill patients.

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. Previously, these patients required vagotomy and extraordinarily high doses of H2 antagonists, which still resulted in suboptimal acid suppression. With PPIs, excellent acid suppression can be achieved in all patients.

Adverse Effects

PPIs are extremely safe. 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. PPIs are not teratogenic in animal models; however, safety during pregnancy has not been established.

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

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

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.

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.

Prostaglandin Analogs

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. 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

Bismuth subcitrate potassium: 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* and are used in 4-drug regimens for the eradication of *H pylori* infection.

Regimen for the treatment of H. pylori-induced 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 is a 14-day regimen of "triple therapy" consisting of **two antibiotics and a PPI**. After completion of triple therapy, the PPI should be continued for a total of 4–6 weeks to ensure complete ulcer healing. 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.* Antibiotics commonly used for H. pylori eradication are clarithromycin, amoxicillin and metronidazole. Another regimen consists of a PPI combined with bismuth subsalicylate, tetracycline and metronidazole for 10–14 days. Bismuth-based quadruple therapies are commonly used as second-line therapies.

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 blockers. Antacids are used commonly by patients as nonprescription remedies for the treatment of intermittent heartburn and dyspepsia. 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). 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. 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, Alka Seltzer) 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. 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.