HISTORY

For more than a century, peptic ulcer disease has been a major cause of morbidity and mortality. In the early part of the 20th century, when stress and diet were judged to be important pathogenetic factors for peptic ulceration, patients with peptic ulcers were treated with hospitalization, bed rest, and the prescription of “bland” diets. By the 1950s, investigators and clinicians had focused their attention primarily on the pathogenetic role of gastric acid, and antacid therapy had become the treatment of choice for peptic ulcer disease. Antacids given at very high doses healed about 80% of duodenal ulcers after 4 weeks of therapy in comparison with placebo. The histamine H2 receptor antagonist cimetidine became available for clinical use in 1977. H2 receptor antagonists produced good ulcer healing rates, ranging from 80% to 95%, after 6 to 8 weeks of therapy. Acid suppression with antisecretory therapy rapidly emerged as the treatment of choice for patients with peptic ulcer disease. With the advent of proton pump inhibitors (PPIs) in the 1980s, even more potent acid suppression and higher rates of ulcer healing could be achieved. Although most acute peptic ulcerations healed with acid suppression therapy, the majority of patients experienced recurrences within 1 year of discontinuing treatment with antacids or antisecretory agents alone. For most of the 20th century, therefore, peptic ulcer disease was considered a chronic, incurable disorder characterized by frequent exacerbations and remissions.

The discovery of the link between Helicobacter pylori and peptic ulcer by Marshall and Warren in the mid-1980s led to another revolution in ulcer therapy. Now there is overwhelming evidence to support H. pylori infection as the most important cause of duodenal and gastric ulcers worldwide. Curing the infection not only heals peptic ulcer but also prevents ulcer relapse.

Although hospitalizations for uncomplicated peptic ulcers in western countries had begun to decline by the 1950s, there was an increase in admissions for ulcer hemorrhage and perforation among the elderly. This increase has been attributed to the greater use of non-steroidal anti-inflammatory drugs (NSAIDs) and low-dose aspirin. The widespread use of NSAIDs has led to an epidemic of ulcer complications and deaths. In the United States, use of prescription NSAIDs accounts for about 25% of all reported adverse drug reactions. Cotherapy with antiulcer drugs and the replacement of NSAIDs with cyclooxygenase-2 (COX-2) inhibitors have become acceptable treatments for patients who are at risk for peptic ulcer disease.

With the declining prevalence of H. pylori infection, the proportion of patients with idiopathic ulcers is growing, at least in the United States, where the reported proportion is between 20% and 30%. In Asia, the proportion of idiopathic ulcers is much lower, at 1% to 4%. It has been argued that as the incidence of H. pylori ulcers falls, a greater proportion of idiopathic ulcers will be seen. In a 5-year cohort of 435 patients with duodenal ulcer described in a study published in 1993, only 6 patients were identified to have H. pylori-negative idiopathic duodenal ulcers. Their serum gastrin responses and peak gastric acid output values were significantly higher than those of H. pylori-negative controls without ulcers. Thus, long-term prophylaxis with antisecretory drugs is advisable (see later), although this recommendation is not evidence-based.

ANTISECRETORY AND ACID-NEUTRALIZING AGENTS
Before the discovery of *H. pylori* as a causal factor in peptic ulcer disease, antiulcer drugs were the mainstays of treatment. Antiulcer therapy is not routinely required for patients with uncomplicated *H. pylori* ulcers in whom the bacterium is successfully eradicated, but antiulcer drugs do play an important role in promoting healing of large ulcers, preventing early recurrent bleeding after endoscopic therapy for bleeding ulcers, reducing the risk of ulcer relapse associated with NSAIDs, and treating idiopathic ulcers. Specific therapies for peptic ulcer are discussed in the following sections.

**ANTACIDS**

**Mechanisms of Action**

Peterson and coworkers showed in 1977 that a liquid antacid preparation of magnesium–aluminum hydroxide, administered in a dosage of 30 mL 1 and 3 hours after meals and at bedtime (approximately 1000 mmol neutralizing capacity per day) was more effective than placebo for hastening the healing of duodenal ulcer. Although it was thought at the time that antacids promote ulcer healing by neutralizing gastric acid, later studies showed that far smaller doses of antacids (as low as 120 mmol per day) had virtually identical efficacy for healing peptic ulcerations. The precise mechanisms by which antacids hasten the healing of peptic ulcerations are not clear, but a variety of cytoprotective effects have been proposed for these agents, especially those that contain aluminum.

**Adverse Effects**

For the magnesium-containing agents, the most common side effect is diarrhea. In contrast, antacids that contain aluminum hydroxide primarily, and those that contain calcium, may cause constipation. Some individuals still use baking soda (sodium bicarbonate) as an antacid, but the use of this agent should be discouraged because of its propensity for causing fluid overload (owing to sodium retention) and alkalosis in susceptible patients (e.g., those with renal insufficiency). All of the antacids must be used with caution, if at all, in patients who have renal insufficiency. In such patients, magnesium-containing agents can cause hypermagnesemia, and the use of calcium carbonate can cause hypercalcemia, alkalosis, and further renal impairment (milk-alkali syndrome). Studies have documented higher plasma concentrations of aluminum in patients with chronic renal insufficiency who were treated with aluminum hydroxide antacids, and it has been proposed that the long-term use of such agents could cause aluminum neurotoxicity in this setting.

Because of the better efficacy and safety profile of new antiulcer drugs, antacids are used nowadays mainly for the relief of dyspepsia. However, many clinicians still prescribe antacids as cotherapy for patients taking NSAIDs, for symptom relief and prevention of ulcers. Later evidence has suggested that co-prescription of NSAIDs with antacids raised the risk of ulcer complications by more than two-fold. This finding was attributed to the possibility that antacids might have masked the dyspeptic symptoms, thereby creating a false sense of protection and raising the risk of silent ulcer complications. Coprescription of antacids in patients taking NSAIDs who are at risk for ulcer should be discouraged.

**HISTAMINE H2 RECEPTOR ANTAGONISTS**

**Mechanisms of Action**
Currently, four H₂ receptor antagonists are available—cimetidine (Tagamet), ranitidine (Zantac), famotidine (Pepcid), and nizatidine (Axid). All four agents are available without prescription (over the counter) in the United States. They share an aromatic ring system and a flexible side chain. These compounds are competitive inhibitors of histamine-stimulated acid secretion, although famotidine appears to have some component of noncompetitive inhibition as well. In addition to blocking histamine-stimulated gastric acid secretion, all four agents suppress basal acid output as well as acid output stimulated by meals (see Chapter 47).

**Pharmacokinetics**

The H₂ receptor antagonists are well absorbed after oral dosing, and absorption is not affected by food. Peak blood levels are achieved within 1 to 3 hours after an oral dose. These drugs are well distributed throughout the body, and all cross the blood-brain barrier and the placenta. After oral administration, cimetidine, ranitidine, and famotidine undergo first-pass hepatic metabolism, which reduces their bioavailability by 35% to 60%. In contrast, nizatidine does not undergo first-pass metabolism, and its bioavailability approaches 100% with oral dosing. When administered in the evening, the drugs are especially effective in suppressing basal acid output at night. This effect appears to be particularly important, because the healing rate for peptic ulcers with antisecretory therapy correlates strongly with the level of reduction in nocturnal gastric acidity.

All four H₂ receptor antagonists are eliminated by a combination of renal excretion and hepatic metabolism. The renal excretion is accomplished both by glomerular filtration and by tubular secretion of the agents. Sixty percent to 80% of orally administered cimetidine, ranitidine, or famotidine is cleared by the liver, whereas the elimination of oral nizatidine is accomplished primarily through renal excretion. After intravenous administration, in contrast, all four agents are eliminated principally through renal excretion. Plasma concentrations of H₂ receptor antagonists are affected by renal insufficiency. It is recommended that the doses be cut in half for patients whose creatinine clearance is 15 to 30 mL/min for cimetidine and famotidine or less than 50 mL/min for nizatidine and ranitidine. Dialysis does not remove substantial amounts of the H₂ receptor antagonists, so dose adjustments for dialysis are not necessary. Liver failure has been found to prolong the half-life of cimetidine, but dose reductions are generally not needed for patients with hepatic failure unless it is accompanied by renal insufficiency.

**Adverse Effects**

The H₂ receptor antagonists are a remarkably safe and well-tolerated group of agents. The overall incidence of side effects is less than 4%, and serious side effects are decidedly uncommon. One meta-analysis of randomized clinical trials concluded that the overall rate of adverse effects reported for the H₂ blockers did not differ significantly from that for placebo. Nevertheless, a number of untoward effects have been described, primarily in anecdotal reports and uncontrolled series. Most attention regarding adverse events has focused on cimetidine, probably because it was the first H₂ receptor antagonist released for clinical use and because it has undergone the most extensive postmarketing surveillance.
Cimetidine has weak antiandrogenic activity that occasionally can cause gynecomastia and impotence. With short-term, standard-dose therapy, these effects are rare. A variety of central nervous system (CNS) symptoms have been reported rarely in patients taking H$_2$ receptor antagonists, including headaches, restlessness, somnolence, dizziness, depression, memory problems, confusion, psychosis, and hallucinations. Myelosuppression is an uncommon, presumably idiosyncratic side effect of the H$_2$ receptor antagonists. In one large series of patients with bone marrow transplants, however, ranitidine was implicated as a possible cause of myelosuppression in 5%. The contribution of ranitidine to the bone marrow suppression in such patients is not clear, but pending further data, it seems prudent to avoid the use of H$_2$ receptor antagonists in bone marrow transplant recipients. The H$_2$ receptor antagonists can cause mild, asymptomatic elevations in the serum levels of hepatic aminotransferases (up to a three-fold increase). These mild laboratory abnormalities may resolve spontaneously, even if the H$_2$ blocker therapy is continued. In all reports, the hepatitis has resolved with discontinuation of the drug.

**Drug Interactions**

Potentially important drug interactions have been described for cimetidine and to a lesser extent for ranitidine. Both of these agents bind to the hepatic cytochrome P-450 (CYP) mixed-function oxidase system, and this binding can inhibit the elimination of other drugs that are metabolized through the same system, including theophylline, phenytoin, lidocaine, quinidine, and warfarin. Consequently, toxic blood levels of these drugs could result from the coadministration of cimetidine or ranitidine. Famotidine and nizatidine have no significant avidity for the CYP system, and these agents do not appear to have any important drug interactions. Even with cimetidine, the agent with the highest affinity for CYP, important drug interactions are uncommon. Nevertheless, if an H$_2$ receptor antagonist is needed for a patient who is taking theophylline, phenytoin, lidocaine, quinidine, or warfarin, it seems prudent to use either famotidine or nizatidine.

**Tolerance and Rebound Acid Hypersecretion**

Tolerance to the antisecretory effects of H$_2$ receptor antagonists appears to develop quickly and frequently. This tolerance could not be overcome by increasing the infusion of ranitidine, even to doses higher than 500 mg per 24 hours. A similar development of tolerance has been observed with the use of orally administered H$_2$ receptor antagonists. The mechanisms that mediate tolerance to the antisecretory effects of H$_2$ receptor antagonists are not entirely clear, but some data suggest that this tolerance is associated with the up-regulation of enterochromaffin-like (ECL) cell activity that accompanies the hypergastrinemia induced by antisecretory therapy (see the section on PPIs).

There are contradictory reports on whether rebound hypersecretion of gastric acid occurs after discontinuation of H$_2$ receptor antagonist therapy. The rebound elevation in nocturnal gastric acid output is short-lived, disappearing by 9 days after the termination of treatment. The mechanism is not known, but the hypersecretion may be a manifestation of transiently up-regulated ECL cell activity.

**PROTON PUMP INHIBITORS**
Mechanism and Site of Action

The PPIs are a class of drugs that decrease gastric acid secretion through inhibition of H,K-ATPase, the proton pump of the parietal cell (see Chapter 47). Currently, five PPIs are used widely as antisecretory agents—omeprazole (Prilosec), esomeprazole (Nexium; the S optical isomer of omeprazole), lansoprazole (Prevacid), pantoprazole (Protonix), and rabeprazole (Aciphex). These compounds, all substituted benzimidazoles, are weak bases, with a pKa of approximately 4.0 for omeprazole, lansoprazole, and pantoprazole, and approximately 5.0 for rabeprazole. These agents are prodrugs that must be activated by acid to effect inhibition of H,K-ATPase. However, the prodrugs are acid-labile compounds that must be protected from degradation by stomach acid during oral administration.

Pharmacokinetics

The PPIs are well absorbed after oral dosing, and the simultaneous administration of antacids does not appear to affect their bioavailability. Food may delay the absorption of lansoprazole, pantoprazole, and rabeprazole, but this delay does not alter the area under the plasma concentration–time curve, which is a key factor in achieving clinical efficacy for these agents. Absorption of the enteric-coated agents may be erratic, and peak serum concentrations are not achieved until 2 to 5 hours after oral administration. Although the plasma half-life of the PPIs is short (<2 hours), the duration of acid inhibition is long (>24 hours) as a result of covalent binding to the H,K-ATPase.

Newer PPIs inhibit H,K-ATPase more rapidly than omeprazole, and emerging clinical data support potential clinical benefits resulting from this pharmacologic property. All PPIs undergo significant hepatic metabolism. Because there is no direct toxicity from PPIs, dose adjustments are not required even in patients with significant renal or hepatic impairment. However, there are significant genetic polymorphisms for one of the CYP isoenzymes involved in PPI metabolism, CYP2C19. Approximately 3% of white persons and 15% of Asians are deficient in CYP2C19. This polymorphism has been shown to substantially raise plasma levels of omeprazole, lansoprazole, and pantoprazole but not those of rabeprazole.

As a result of their requirement for concentration and activation in acidic compartments, the PPIs bind predominantly to those proton pumps that are actively secreting acid. Thus, the efficacy of the PPIs for inhibiting acid secretion is limited if they are administered during the fasting state, when only approximately 5% of the stomach's proton pumps are active. With meal stimulation, in contrast, 60% to 70% of the proton pumps actively secrete acid. Thus, the PPIs are most effective if they are administered immediately before meals. For once-daily dosing, it is recommended that the PPIs be taken immediately before breakfast. Eradication of H. pylori infection has been found to render PPIs somewhat less effective in elevating the gastric pH in patients with duodenal ulcer. The mechanism by which H. pylori infection augments the pH-elevating effect of the PPIs is not clear. Conceivably, this phenomenon might be a consequence either of alkaline ammonia produced from urea by the organism or, more likely, of the greater gastric bicarbonate secretion and lesser gastric acid secretion associated with ongoing infection.

Adverse Effects
The PPIs are a remarkably safe and well-tolerated group of agents. The most commonly reported side effects are headache and diarrhea, yet the rate at which patients experience these symptoms does not differ significantly from that for patients treated with placebo.\(^\text{[11]}\)

**Drug Interactions**

The elevation of gastric pH induced by the PPIs can affect the absorption of a number of medications. However, this antisecretory action rarely has clinically important effects on drug pharmacokinetics, except when the PPIs are given with ketoconazole or digoxin.\(^\text{[12]}\) Ketoconazole requires stomach acid for absorption, and this drug may not be absorbed effectively after PPIs have inhibited gastric acid secretion. Conversely, an elevated gastric pH facilitates the absorption of digoxin, resulting in higher plasma levels of this agent. If a patient requires both PPI and antifungal therapy, it is recommended that an agent other than ketoconazole be chosen. For patients treated concomitantly with PPIs and digoxin, clinicians should consider monitoring plasma digoxin levels.

Because the PPIs are metabolized by the CYP system, there is potential for them to alter the metabolism of other drugs that are eliminated by CYP enzymes. Among the available PPIs, omeprazole appears to have the greatest potential for such drug interactions and has been shown to delay the clearance of warfarin, diazepam, and phenytoin.\(^\text{[13]}\) Lansoprazole, pantoprazole, and rabeprazole do not appear to interact significantly with drugs metabolized by the CYP system. Even with omeprazole, however, clinically important drug interactions are uncommon.

**Impact of Proton Pump Inhibitor–Induced Hypergastrinemia**

PPIs and other antisecretory agents cause hypergastrinemia by inhibiting gastric acid secretion. The rise in serum gastrin levels is usually modest. The elevated gastrin values return to normal within 4 weeks after PPI therapy is discontinued. In addition to stimulating acid secretion, gastrin has been shown to have trophic effects on the gastrointestinal (GI) mucosa. In the stomach, these trophic effects are manifested predominantly in the ECL cells. Female rats in which protracted hypergastrinemia has been induced by treatment with PPIs also have ECL cell hyperplasia and gastric carcinoid tumors.\(^\text{[14]}\) However, there are no reports of gastric carcinoid tumors attributable to antisecretory therapy in humans. Even in patients with Zollinger-Ellison syndrome who have severe hypergastrinemia, carcinoid tumors are uncommon and occur predominantly in patients with multiple endocrine neoplasia (MEN).\(^\text{[15]}\)

**Impact of Proton Pump Inhibitors on Patients Infected with Helicobacter pylori**

Some data suggest that the long-term administration of PPIs to patients who are infected with *H. pylori* might accelerate the development of atrophic gastritis. *H. pylori* infection is the major cause of chronic active gastritis, a condition that can lead to gastric atrophy, intestinal metaplasia, and adenocarcinoma of the stomach (see Chapters 48 and 49). Studies have shown that PPI therapy can alter this pattern so that the most intense inflammatory changes involve the gastric body and fundus.\(^\text{[16]}\) In theory, this shift from antral-predominant to gastric body–predominant inflammation induced by PPI therapy might cause atrophy of the acid-producing portion of the stomach.
A study conducted in the Netherlands and Sweden explored the development of atrophic gastritis in patients with severe gastroesophageal reflux disease (GERD) treated with either long-term omeprazole therapy or antireflux surgery (fundoplication). After a mean period of 5 years of PPI therapy, 31% of the *H. pylori*-positive patients in the Netherlands had atrophic gastritis. In contrast, none of the 72 Swedish patients who were treated with fundoplication, including 31 who had *H. pylori* infection, had atrophic gastritis during a similar period of follow-up. This study has been criticized for a number of deficiencies. The investigation was not a randomized, controlled trial but rather a comparison of two different cohorts, with different mean ages, treated in different countries. Authorities have questioned the validity and importance of the histologic criteria used by the study pathologists for grading atrophic gastritis, and none of the patients in either group had intestinal metaplasia, the lesion thought to be the precursor of gastric adenocarcinoma. A subsequent, large Scandinavian study of patients with gastroesophageal reflux disease has found no difference in the development of gastric atrophy between those treated for 3 years with long-term PPI therapy and those treated with antireflux surgery. The members of the U.S. Food and Drug Administration (FDA) advisory group concluded that the available data did not establish such an effect, and did not recommend routine treatment of *H. pylori* before initiation of PPI therapy.

**Tolerance and Rebound Acid Hypersecretion**

Tolerance to the antisecretory effects of PPI therapy has not been seen during short-term investigations. Rebound acid hypersecretion after PPI therapy has been shown for both basal and maximal acid output by 14 days after cessation of treatment. Rebound hypersecretion is found in *H. pylori*-negative, but not *H. pylori*-positive, subjects, possibly owing to the influence of the enhanced oxyntic gastritis that occurs during PPI therapy. The phenomenon can persist for at least 2 months after prolonged treatment. It has been suggested that PPI-induced hypergastrinemia exerts trophic effects on the oxyntic mucosa. The clinical relevance of this phenomenon remains unknown.

**MUCOSA-PROTECTIVE AGENTS**

**Sucralfate**

**Mechanisms of Action**

Sucralfate (Carafate) is a complex metal salt of sulfated sucrose. Although the sucralfate molecule contains aluminum hydroxide, the agent has little acid-neutralizing capacity. When exposed to gastric acid, the aluminum hydroxide dissociates, leaving sulfate anions that can bind electrostatically to positively charged proteins in damaged tissue. In this fashion, sucralfate adheres to ulcer craters, where it appears to form a protective barrier that may prevent further acid-peptic attack. Other proposed beneficial effects of sucralfate are enhancement of mucosal prostaglandin levels, stimulation of mucus and bicarbonate secretion, binding of bile salts, binding of epidermal growth factors, and promotion of angiogenesis.

Sucralfate has demonstrated efficacy (similar to that of the H2 receptor antagonists) in healing duodenal ulcer when given in a dose of 1 g four times daily. The drug has demonstrated efficacy in the treatment of gastric ulcer as well, but sucralfate has not been approved by the FDA for this indication. Compared with the H2 receptor antagonists and the PPIs, however, there is much less published experience with sucralfate.
Pharmacokinetics

Less than 5% of the sucralfate administered is absorbed owing to its poor solubility. The drug is excreted in feces. The high aluminum content causes a small but significant rise in serum and urine aluminum levels within 2 days. In patients with normal renal function, the minor amounts of aluminum absorption with short-term therapy are of no clinical significance.

Toxicity and Drug Interactions

Because of the lack of systemic absorption, sucralfate appears to have no systemic toxicity. Gastric bezoar formation has been reported uncommonly. Concern has been raised about the potential for aluminum neurotoxicity in patients with chronic renal failure. However, the impact on the disposition of aluminum in the body has not been adequately studied in renal failure. Sucralfate is best avoided in this population. The drug can bind to a number of medications, including phenytoin and warfarin, reducing their absorption. Important drug interactions appear to be rare, however, and can be avoided entirely if sucralfate is administered separately from other medications.

Bismuth

Mechanisms of Action

Bismuth preparations have been used widely to treat diarrhea, abdominal pain, and dyspepsia for hundreds of years. Two colloidal preparations of bismuth have been most commonly used, colloidal bismuth subcitrate and bismuth subsalicylate (e.g., Pepto-Bismol). These agents have some demonstrated efficacy in healing peptic ulcers, but the mechanisms underlying this therapeutic effect are not clear. The bismuth forms complexes with mucus that appear to coat ulcer craters, perhaps affording protection from acid-peptic attack. Effects on increasing mucosal prostaglandin synthesis and bicarbonate secretion also have been proposed, and bismuth has documented antimicrobial actions against H. pylori. Bismuth has been approved by the FDA for use in combination with other agents for the treatment of H. pylori infection (see Chapter 48).

Pharmacokinetics

Bismuth is largely unabsorbed and is excreted in the feces. Colonic bacteria convert bismuth subcitrate and bismuth subsalicylate to bismuth sulfide, which turns the stools black. Trace amounts of bismuth are absorbed in the upper GI tract. Absorbed bismuth is slowly excreted in the urine for 3 months or longer.

Toxicity

Short-term, standard-dose therapy with bismuth appears to carry little risk of toxicity. However, there is the potential for bismuth neurotoxicity if the agent is given for extended periods in high dosage, especially in patients with renal failure.

Prostaglandin E Analogs

Mechanisms of Action
Endogenous prostaglandins, including prostaglandin E₂ (PGE₂), regulate mucosal blood flow, epithelial cell proliferation, epithelial restitution, mucosal immunocyte function, mucus and bicarbonate secretion, and basal acid secretion. There is substantial evidence that the ulcerogenic effect of an NSAID correlates well with its ability to suppress prostaglandin synthesis (see Chapter 50). Misoprostol, a prostaglandin E₁ analog, is the only prostaglandin analog approved by the FDA for the prevention of NSAID-induced ulcer disease. The drug not only enhances mucosal defense mechanisms but also inhibits gastric acid secretion. After binding to the prostaglandin receptor on the parietal cell, misoprostol inhibits gastric acid secretion in a dose-dependent manner that is mediated through inhibition of histamine-stimulated cyclic adenosine monophosphate (cAMP) production. It has been shown that misoprostol significantly reduces nocturnal, basal, and meal-stimulated acid secretion at a standard therapeutic dose, although the effect is not as potent as that of antisecretory agents.

**Pharmacokinetics**

Misoprostol is well absorbed after oral administration. The plasma concentration peaks at about 30 minutes, with a serum half-life of approximately 1.5 hours. The drug has no effect on hepatic cytochrome P-450. Misoprostol metabolites are excreted in the urine, but dose reduction is unnecessary in patients with chronic renal failure.

**Toxicity**

Dose-related diarrhea is the most common side effect, occurring in up to 30% of patients and limiting the usefulness of misoprostol. Diarrhea is related to prostaglandin-induced increases in intestinal water and electrolyte secretion or acceleration of intestinal transit time. Administration of misoprostol with food may reduce diarrhea. Prostaglandins stimulate uterine smooth muscle. Uterine bleeding has been reported with prostaglandin analogs during the first trimester of pregnancy. Misoprostol is therefore contraindicated in women who may be pregnant.