Chapter 63
Drugs Used in the Treatment of Gastrointestinal Diseases
DRUGS USED IN ACID-PEPTIC DISEASES

1. **classification of drugs**

2. **agents that reduce intragastric acidity**
   
   Antacids, H$_2$ antagonists, Proton pump inhibitors (PPI)

3. **mucosal protective agents**
   
   sucralfate, prostaglandin analogs, colloidal bismuth compounds
[Aims]

- **Knowing of** pathogenesis and medication principle of peptic ulcer.
- **Mastering** classification of drugs used in acid-peptic diseases
- **Mastering** feature and application principle of antacids.
- **Mastering** mechanism of action, clinical application and main adverse reaction of every variety of acid secretion inhibitors.
- **Knowing of** pharmacological action and clinical application of mucosal protective agents and anti-Hp agents.
I. DRUGS USED IN ACID-PEPTIC DISEASES

Acid-peptic diseases include

- gastroesophageal reflux,
- peptic ulcer (gastric and duodenal),
- and stress-related mucosal injury.
The pathogenesis of peptic ulcer is caused by the **imbalance** between aggressive and protective factors.
Risk Factors of Gastric Ulcer

gastric acid, pepsin, bile
infection of Helicobacter pylori
NSAIDS (nonsteriodal anti-inflammatory drugs)
smoking, alcohol, strain
- **aggressive factors** (acid, pepsin, bile)
- **defensive factors** (mucus and bicarbonate secretion, prostaglandins, blood flow, and the processes of restitution and regeneration after cellular injury)

- erosions or ulceration:

  **aggressive factors > defensive factors**
Over 99% of peptic ulcers are caused by

- infection with the bacterium *Helicobacter pylori*
- or by use of nonsteroidal anti-inflammatory drugs (NSAIDs).
1. Weakening of the aggressive factors

Weakening ways include (a) neutralizing of the over-secretion of stomach acid; (b) blockade of HCl secretion; (c) antibiotic therapy (Helicobacter pylori).

2. Strengthening of the protective factors

Strengthening methods include: (a) coating of the gastrointestinal mucosa; and (b) increasing of mucus and HCO$_3^-$ salt secretion.

HCl: hydrochloric acid, HCO$_3^-$: bicarbonate
Classification of drugs

- agents that reduce intragastric acidity
- agents that promote mucosal defense
AGENTS THAT REDUCE INTRAGASTRIC ACIDITY
PHYSIOLOGY OF ACID SECRETION
Gastric acid secretion is under the control of three principal agonists histamine, acetylcholine, and gastrin. The final common pathway is through the proton pump, H\(^+\)/K\(^+\) ATPase.
AGENTs THAT REDUCE INTRAGASTRIC ACIDITY

Classification of drugs

A. Antacids
B. H₂ antagonists
C. Proton pump inhibitors (PPI)
ANTACIDS
Introduction

I. Discovery

- a famous theory of "no acid, no ulcer".
- ease of administration and low cost
- mainstay of treatment for acid-peptic disorders
- only temporary relief of the symptoms
- the relapse rate and complications of peptic ulcers remain intolerantly high.
Sir James W. Black —— histamine receptor antagonist to block histamine-stimulated acid secretion.

_cimetidine_ was developed in Smith Kline & French Pharmaceutical Company in 1976.
cimetidine provided dose-related inhibition of gastric secretion stimulated by injected histamine, insulin, caffeine, protein-rich meals and cholinergic muscarinic drugs.

Cimetidine became the world's number one prescription drug in last several years and estimated a cost of £1 billion in worldwide prescription by 1983.
Pharmacological effects

- neutralize over-production of gastric acids

Gastric antacids are weak bases that react with gastric hydrochloric acid ($\text{HCl}$) to form a salt and water.

Their usefulness in peptic ulcer disease appears to lie in their ability to reduce gastric acidity and, since pepsin is inactive in solutions above pH 4.0, to reduce peptic activity.
they may also promote mucosal defense mechanisms through stimulation of mucosal prostaglandin production.
Sodium bicarbonate

**Adverse reactions**

- Reacts rapidly with HCl to produce carbon dioxide and NaCl (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

Adverse reactions

- 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).
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.
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

- The description of selective histamine H₂-receptor blockade by Black in 1970 was a landmark in the history of pharmacology.
- and set the stage for the modern approach to the treatment of acid-peptic disease, which until then had relied almost entirely on acid neutralization in the lumen of the stomach.
With the recognition of the role of *H pylori* in ulcer disease (which may be treated with appropriate antibacterial therapy) and the advent of proton pump inhibitors, the use of prescription H₂ blockers has declined markedly.
Chemistry & Pharmacokinetics

- Four H$_2$ antagonists are in clinical use:
  - cimetidine, ranitidine, famotidine, and nizatidine (Figure 63-2).
Figure 63-2. H₂-receptor-blocking drugs.
The serum half-lives of the four agents range from 1.1-4 hours; however, duration of action depends on the dose given (Table 63-1).
### Table 63–1. Clinical comparisons of H₂-receptor blockers.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Relative Potency</th>
<th>Dose to Achieve &gt; 50% Acid Inhibition for 10 Hours</th>
<th>Usual Dose for Acute Duodenal or Gastric Ulcer</th>
<th>Usual Dose for Gastroesophageal Reflux Disease</th>
<th>Usual Dose for Prevention of Stress-Related Bleeding</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cimetidine</td>
<td>1</td>
<td>400–800 mg</td>
<td>800 mg HS or 400 mg bid</td>
<td>800 mg bid</td>
<td>50 mg/h continuous infusion</td>
</tr>
<tr>
<td>Ranitidine</td>
<td>4–10×</td>
<td>150 mg</td>
<td>300 mg HS or 150 mg bid</td>
<td>150 mg bid</td>
<td>6.25 mg/h continuous infusion or 50 mg IV every 6–8 h</td>
</tr>
<tr>
<td>Nizatidine</td>
<td>4–10×</td>
<td>150 mg</td>
<td>300 mg HS or 150 mg bid</td>
<td>150 mg bid</td>
<td>Not available</td>
</tr>
<tr>
<td>Famotidine</td>
<td>20–50×</td>
<td>20 mg</td>
<td>40 mg HS or 20 mg bid</td>
<td>20 mg bid</td>
<td>20 mg IV every 12 h</td>
</tr>
</tbody>
</table>
excretion

- hepatic metabolism, glomerular filtration, and renal tubular secretion.
- Dose reduction: renal (and possibly severe hepatic) insufficiency.
- In the elderly, there is a decline of up to 50% in drug clearance as well as a significant reduction in volume of distribution.
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 (Figure 63-3, P1012).
- highly selective
- The volume of gastric secretion and the concentration of pepsin are also reduced.
two mechanisms

- H₂ antagonists reduce acid secretion stimulated by histamine as well as by gastrin and cholinomimetic agents through two mechanisms.
First, histamine released from enterochromaffin-like cells (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 results in diminished acid secretion in the presence of H$_2$-receptor blockade. It appears that reduced parietal cell cAMP levels attenuate the intracellular activation of protein kinases by gastrin or acetylcholine.
When given in usual prescription doses, all of the H₂ antagonists inhibit **60-70%** of total 24-hour acid secretion.
- $H_2$ antagonists are especially effective at inhibiting nocturnal acid secretion (which depends largely on histamine).
- but have a modest impact on meal-stimulated acid secretion (which is stimulated by gastrin and acetylcholine as well as histamine). Thus, they block more than 90% of nocturnal acid but only 60-80% of daytime acid secretion.
Recommended prescription doses maintain greater than 50% acid inhibition for 10 hours; hence, these drugs are commonly given twice daily.
Clinical Uses
A. Gastroesophageal Reflux Disease (GERD)

- take either antacids or intermittent $H_2$ antagonists.

<table>
<thead>
<tr>
<th></th>
<th><strong>Speed</strong> of symptom relief</th>
<th><strong>Time</strong> of symptom relief</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Antacids</strong></td>
<td>fast</td>
<td>short-lived (1-2 hours)</td>
</tr>
<tr>
<td><strong>$H_2$ antagonists</strong></td>
<td>prophylactical</td>
<td>long-lived (6-10 hours)</td>
</tr>
</tbody>
</table>
In patients with erosive esophagitis (approximately half of patients with GERD), H₂ antagonists afford healing in less than 50% of patients.

Although higher doses of H₂ antagonists increase healing rates, proton pump inhibitors are preferred.
B. Peptic Ulcer Disease

- Proton pump inhibitors have largely replaced H$_2$ antagonists in the treatment of peptic ulcer disease.
Nocturnal acid suppression by either drug group affords effective ulcer healing in the majority of patients with uncomplicated gastric and duodenal ulcers.

Hence, all the agents may be administered once daily at bedtime for acute, uncomplicated ulcers, resulting in ulcer healing rates greater than 80-90% after 6-8 weeks of therapy.
For the minority of patients in whom *H. pylori* cannot be successfully eradicated, H$_2$ antagonists may be given daily at bedtime in half of the usual ulcer therapeutic dose to prevent ulcer recurrence (eg, ranitidine, 150 mg; famotidine, 20 mg).
For patients with ulcers caused by aspirin or other NSAIDs, $H_2$ antagonists provide rapid ulcer healing so long as the NSAID is discontinued.

If the NSAID must be continued for clinical reasons despite active ulceration, a proton pump inhibitor should be given to promote ulcer healing.
C. Nonulcer Dyspepsia
D. Prevention of Bleeding from Stress-Related Gastritis

- $\text{H}_2$-receptor antagonists significantly reduce the incidence of bleeding from stress-related gastritis in seriously ill patients in the intensive care unit (ICU).
Adverse Effects

- extremely safe
- diarrhea, headache, fatigue, myalgias, and constipation
A. Central Nervous System

- Mental status changes (confusion, hallucinations, agitation) may occur with administration of intravenous $H_2$ 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.
B. Endocrine Effects

- **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.
C. Pregnancy and Nursing Mothers

- 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.
D. Other Effects

- rarely
- blood dyscrasias
- bradycardia
- reversible abnormalities in liver chemistry
Drug interactions

- Cimetidine interferes with several important hepatic cytochrome P450 drug metabolism pathways, including those catalyzed by CYP1A2, CYP2C9, CYP2D6, and CYP3A4.
- Hence, the half-lives of drugs metabolized by these pathways may be prolonged.
All of these agents except famotidine inhibit gastric first-pass metabolism of ethanol, especially in women.

Increased bioavailability of ethanol could lead to increased blood ethanol levels.
PROTON PUMP INHIBITORS (PPI)

- They are now among the most widely selling drugs worldwide due to their outstanding efficacy and safety.
Parietal cells' H⁺ ion secretion depends on an H⁺,K⁺-ATPase pump promoting H⁺, K⁺ exchange.

- Five proton pump inhibitors are available for clinical use: omeprazole, lansoprazole, rabeprazole, pantoprazole, and esomeprazole.
- All are available in oral formulations. Esomeprazole, lansoprazole, and pantoprazole are also available in intravenous formulations.
- oral products are formulated for delayed release as acid-resistant, enteric-coated capsule or tablet formulations.

- For children or patients with dysphagia or enteral feeding tubes, capsules may be opened and the microgranules mixed with apple or orange juice or mixed with soft foods (eg, applesauce).
bioavailability

- The bioavailability of all agents is decreased approximately 50% by food; hence, the drugs should be *administered on an empty stomach.*
Proton pump inhibitors should be administered approximately **1 hour before a meal** (usually breakfast or dinner), 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; however, the duration of acid inhibition lasts up to 24 hours due to the irreversible inactivation of the proton pump.
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.
Proton pump inhibitors undergo rapid first-pass and systemic hepatic metabolism and have negligible renal clearance.

Dose reduction is not needed for patients with renal insufficiency or mild to moderate liver disease but should be considered in patients with severe liver impairment.
From a pharmacokinetic perspective, proton pump inhibitors are *ideal drugs*:

- *short serum half-life,*
- *concentrated and activated near their site of action,*
- *long duration of action.*
Pharmacodynamics

- In contrast to H₂ antagonists, proton pump inhibitors inhibit both fasting and meal-stimulated secretion because they block the final common pathway of acid secretion, the proton pump.

- In standard doses, proton pump inhibitors inhibit 90-98% of 24-hour acid secretion.
Clinical Uses

- A. Gastroesophageal Reflux Disease (GERD)
- B. Peptic Ulcer Disease
- C. Nonulcer Dyspepsia
- D. Prevention of Stress-Related Mucosal Bleeding
- E. Gastrinoma and Other Hypersecretory Conditions
A. Gastroesophageal Reflux Disease (GERD)

- Proton pump inhibitors 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.

- Once-daily dosing provides effective symptom relief and tissue healing in 85-90% of patients; up to 15% of patients require twice-daily dosing.
symptoms recur

- GERD symptoms recur in over 80% of patients within 6 months after discontinuation of a proton pump inhibitor. For patients with erosive esophagitis or esophageal complications, long-term daily maintenance therapy with a full-dose or half-dose proton pump inhibitor is usually needed.
first-line therapy

- Due to recent cost reductions, proton pump inhibitors are increasingly being used as first-line therapy for patients with symptomatic GERD.
B. Peptic Ulcer Disease

- A lesion that occurs primarily in the mucous membrane of the stomach or duodenum; it is produced when external factors reduce the ability of the mucosal lining to resist the acidic effects of gastric juice.

- Until recently the factors responsible for peptic ulcers remained unclear; a stressful lifestyle and rich diet commonly were blamed. Evidence now indicates that infection with the bacterium *Helicobacter pylori* and long-term use of nonsteroidal anti-inflammatory drugs (NSAIDs) are the two major causes of peptic ulcer.
Between 10 and 15 percent of the world's population suffers from peptic ulcer. Duodenal ulcers, which account for 80 percent of peptic ulcers, are more common in men than in women, but stomach ulcers affect women more frequently.

The symptoms of gastric and duodenal ulcer are similar and include a gnawing, burning ache and hungerlike pain in the mid-upper abdomen, usually experienced from one to three hours after meals and several hours after retiring.
In the early 1980s two Australian researchers, Barry Marshall (left) and J. Robin Warren, challenged previous theories of ulcer development with evidence that ulcers could be caused by H. pylori.
Infection with H. pylori is the most common bacterial infection in humans;

it is pervasive in the Third World, and in the United States it affects about a third of the population. Among those who suffer from peptic ulcers, as many as 90 percent of those with duodenal ulcers and 70 percent with gastric ulcers are believed to be infected with H. pylori. Evidence also exists that untreated H. pylori infection may lead to stomach cancer.
The recommended treatments for H. pylori-induced ulcers are antibiotics, such as tetracycline, metronidazole, amoxicillin, and clarithromycin,
and drugs that stop the secretion of stomach acid, including proton pump inhibitors (omeprazole or lansoprazole) and H$_2$ blockers (cimetidine and ranitidine). Bismuth subsalicylate may also be used to protect the lining of the stomach from acid.
Most peptic ulcers not caused by *H. pylori* infection result from the ingestion of large quantities of **NSAIDs**, which often are prescribed for conditions such as rheumatoid arthritis.
Withdrawal of NSAID treatment usually allows the ulcer to heal, but if this is not possible the ulcer can be managed with the H2 blockers cimetidine and ranitidine (marketed as Tagamet and Zantac, respectively) or with the proton pump inhibitors lansoprazole (Prevacid) and omeprazole (Losec or Prilosec).
- A small proportion of peptic ulcers results from the **Zollinger-Ellison syndrome**, an uncommon disease associated with a tumour of the duodenum or pancreas that causes an increase in gastric acid secretion.

- **Cigarette smoking** has been found to have an adverse effect on peptic ulcers, slowing healing and promoting recurrence. Complications of ulcers include bleeding, perforation of the abdominal wall, and obstruction of the gastrointestinal tract.
Compared with H₂ antagonists, proton pump inhibitors afford more rapid symptom relief and faster ulcer healing for duodenal ulcers and, to a lesser extent, gastric ulcers.

All of the pump inhibitors heal more than 90% of duodenal ulcers within 4 weeks and a similar percentage of gastric ulcers within 6-8 weeks.
1. *H. pylori*-associated ulcers

- There are two therapeutic goals: heal the ulcer and eradicate the organism.
- The most effective regimens for *H. pylori* eradication are combinations of two antibiotics and a proton pump inhibitor.
Proton pump inhibitors 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*.
best treatment regimen

- The best treatment regimen consists of a 10-14 day regimen of "triple therapy":
  1. proton pump inhibitor twice daily;
  2. clarithromycin, 500 mg twice daily;
  3. amoxicillin, 1 g twice daily. For patients who are allergic to penicillin, metronidazole, 500 mg twice daily, should be substituted for amoxicillin.
**Attention:** After completion of triple therapy, the proton pump inhibitor should be continued once daily for a total of 4—6 weeks to ensure complete ulcer healing.
2. **NSAID**-associated ulcers

- For patients with ulcers caused by aspirin or other NSAIDs, either \( \text{H}_2 \) antagonists or proton pump inhibitors provide rapid ulcer healing so long as the NSAID is discontinued; continued use of the NSAID impairs ulcer healing.
Treatment with a once-daily proton pump inhibitor promotes ulcer healing despite continued NSAID therapy.
Proton pump inhibitors are also given to prevent ulcer complications from NSAIDs.

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.
3. Prevention of rebleeding from peptic ulcers

- initial bolus administration (60-80 mg) followed by constant infusion (8 mg/h) commonly is recommended.
C. Nonulcer Dyspepsia

- modest efficacy
D. Prevention of Stress-Related Mucosal Bleeding

- Clinically important bleeding from upper gastrointestinal erosions or ulcers occurs in 1-5% of critically ill patients due to mucosal ischemia.
The only proton pump inhibitor approved by the Food and Drug Administration for reduction of stress-related mucosal bleeding is an oral immediate-release omeprazole formulation, which is administered by nasogastric tube twice daily on the first day, then once daily.
E. 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 proton pump inhibitors, excellent acid suppression can be achieved in all patients.

Typical doses of omeprazole are 60—120 mg/d.
Adverse Effect

- **A. General**: extremely safe
- **B. Nutrition**: minor reduction in oral cyanocobalamin (vitamin B₁₂) absorption; no mineral deficiencies have been reported
- **C. Respiratory and Enteric Infections**: Some studies have reported an increased risk of both community-acquired respiratory infections and nosocomial pneumonia among patients taking proton pump inhibitors. A small increased risk of enteric infections may exist.
D. Potential Problems Due to Increased Serum Gastrin:

- The rise in serum gastrin levels in patients receiving long-term therapy with proton pump inhibitors has raised two theoretical concerns.

- First, gastrin is a trophic hormone that stimulates hyperplasia of ECL cells. Carcinoid tumor formation has not been documented.

- Second, hypergastrinemia increases the proliferative rate of colonic mucosa, potentially promoting carcinogenesis.

At present, routine monitoring of serum gastrin levels is not recommended in patients receiving prolonged proton pump inhibitor therapy.
MUCOSAL PROTECTIVE AGENTS

- 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
- PROSTAGLANDIN ANALOGS
- COLLOIDAL BISMUTH COMPOUNDS
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.
Pharmacodynamics form a physical barrier that restricts further caustic damage and stimulates mucosal prostaglandin and bicarbonate secretion.
Clinical Uses

The dosage is 1g four times daily on an empty stomach (at least 1 hour before meals).

Sucralfate also requires an acid pH to be activated and so should not be administered simultaneously with antacids, H$_2$-receptor antagonists, or proton pump inhibitors.

At present, its clinical uses are limited.
PROSTAGLANDIN ANALOGS

- **Misoprostol**, a methyl analog of PGE$_1$
Pharmacodynamics

- Misoprostol has both **acid inhibitory** and **mucosal protective** properties:
  1. stimulate mucus and bicarbonate secretion
  2. enhance mucosal blood flow
  3. binds to a prostaglandin receptor on parietal cells, reducing histamine-stimulated cAMP production and causing modest acid inhibition.
Clinical Uses

- Misoprostol reduces the incidence of **NSAID-induced ulcers** to less than 3% and the incidence of ulcer complications by 50%.
- **Proton pump inhibitors** may be as effective as and better tolerated than misoprostol.
Adverse Effect

- Diarrhea and cramping abdominal pain occurs in 10-20% of patients.
- should not be used during pregnancy or in women of childbearing potential
COLLOIDAL BISMUTH COMPOUNDS
Pharmacodynamics

- Like sucralfate, *coats ulcers and erosions*, creating a protective layer against acid and pepsin.
- It may also *stimulate prostaglandin, mucus, and bicarbonate secretion*.
- Have direct *antimicrobial activity against Hpylori*.
Clinical Uses

- have been used in multidrug regimens for the eradication of *H. pylori* infection.
Adverse Effect

- excellent safety
- blackening of the stool
- darkening of the tongue
- Prolonged usage may rarely lead to bismuth toxicity, resulting in encephalopathy (ataxia, headaches, confusion, seizures).