Drugs Used in Gastrointestinal disorders Part 1

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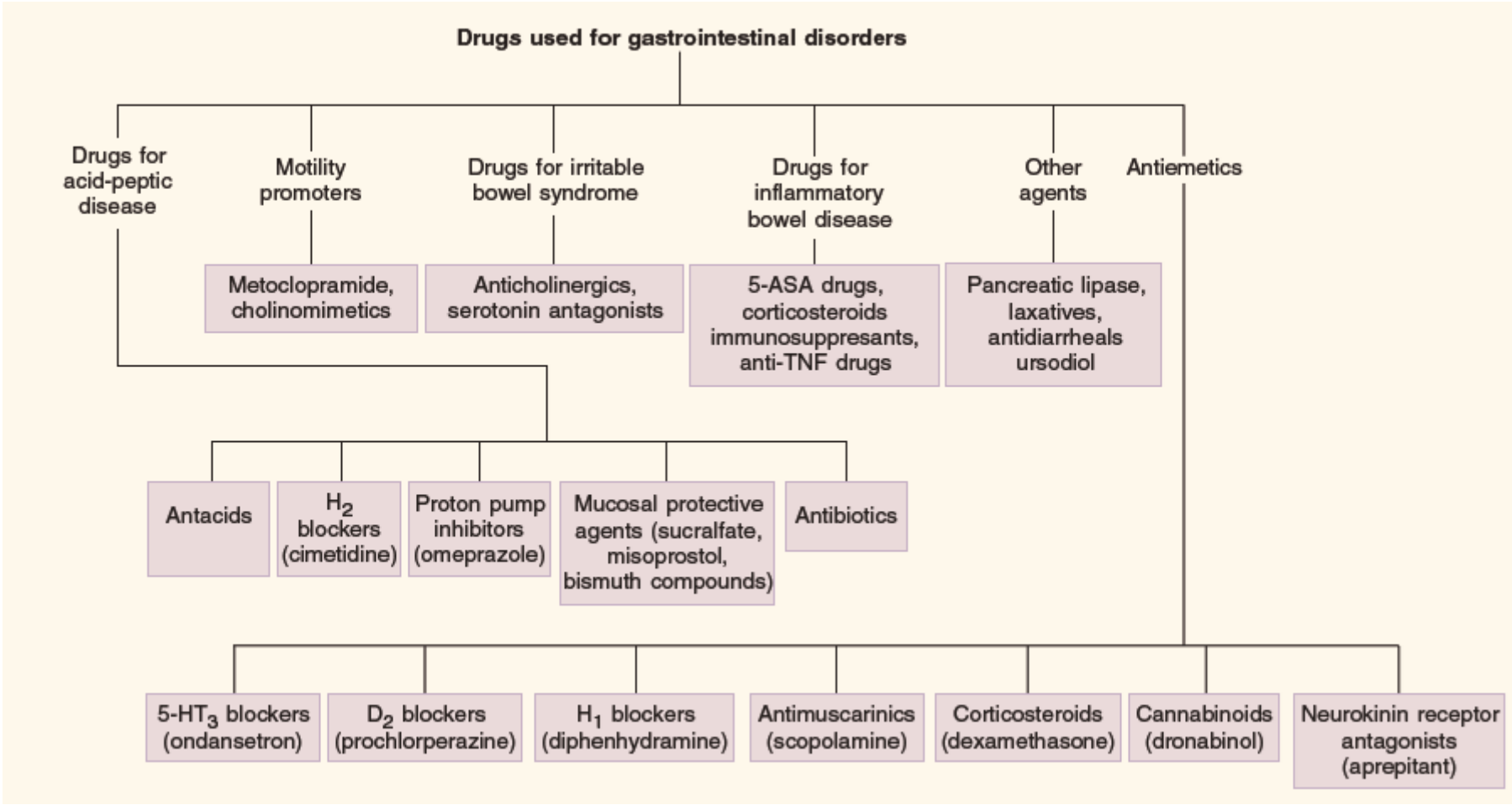
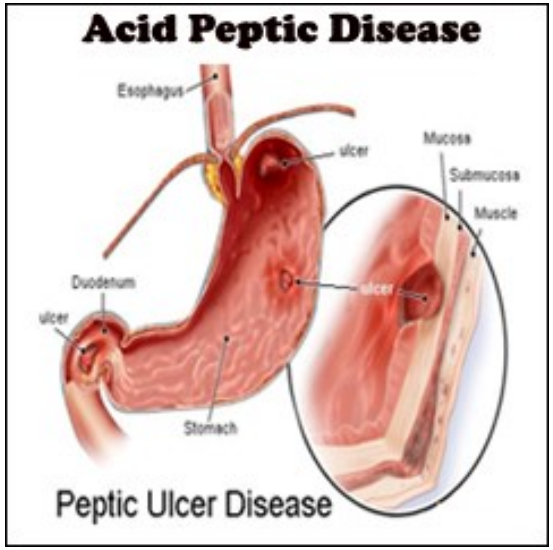

Drugs used for gastrointestinal disorders
Drugs for acid-peptic disease
Motility promoters
Drugs for irritable bowel syndrome
Drugs for inflammatory bowel disease
Other agents
Antiemetics
Metoclopramide, cholinomimetics
Anticholinergics, serotonin antagonists
5-ASA drugs, corticosteroids immunosuppresants, anti-TNF drugs
Pancreatic lipase, laxatives, antidiarrheals ursodiol
Antacids
H2 blockers (cimetidine)
Proton pump inhibitors (omeprazole)
Mucosal protective agents (sucralfate, misoprostol, bismuth compounds)
Antibiotics
5-HT3 blockers (ondansetron)
D2 blockers (prochlorperazine)
H1 blockers (diphenhydramine)
Antimuscarinics (scopolamine)
Corticosteroids (dexamethasone)
Cannabinoids (dronabinol)
Neurokinin receptor antagonists (aprepitant)

A. Acid-Peptic Diseases

- Acid-peptic diseases are a group of disorders involving erosion or ulceration of the mucosal lining of the gastrointestinal tract; includes:
  1. GERD
  2. peptic ulcer (gastric and duodenal ulcers)
  3. nonulcer dyspepsia
  4. stress-related gastritis

- In all these conditions, mucosal erosions or ulceration arise when the caustic effects of aggressive factors (acid, pepsin) overwhelm the defensive factors of the gastrointestinal mucosa (mucus and bicarbonate secretion, prostaglandins).



A. Drugs Used in Acid-Peptic Diseases

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

1) Agents that reduce intragastric acidity:
   1. Antacids
   2. H2 blockers
   3. proton pump inhibitors

2) Agents that promote mucosal defense

3) Or, in the case of peptic ulcers, eradicate the bacterium *Helicobacter pylori*.

(Over 90% of peptic ulcers are caused by infection with the bacterium *Helicobacter pylori* or by use of nonsteroidal anti-inflammatory drugs (NSAIDs)).

Physiology of acid secretion

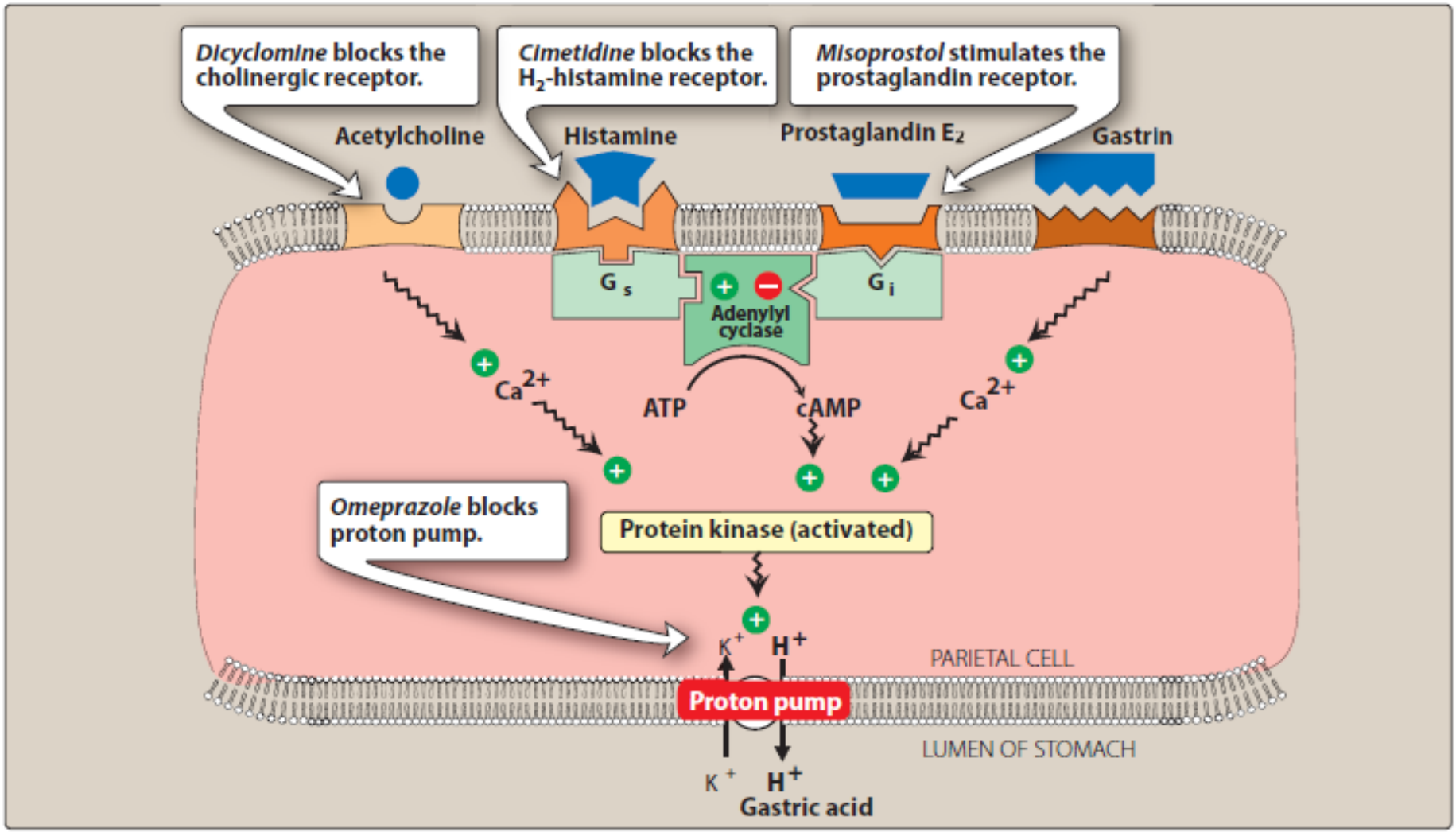


Figure 31.4

Effects of acetylcholine, histamine, prostaglandin E_2, and gastrin on gastric acid secretion by the parietal cells of stomach. G_s and G_i are membrane proteins that mediate the stimulatory or inhibitory effect of receptor coupling to adenylyl cyclase.

Antacids

- 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.
- Because pepsin (a proteolytic enzyme) is inactive at a pH greater than 4, antacids also reduce pepsin activity.
- The efficacy of an antacid depends on its capacity to neutralize gastric HCl and on whether the stomach is full or empty (food delays stomach emptying allowing more time for the antacid to react).

- They include:
  1. Sodium bicarbonate
  2. Calcium carbonate
  3. Magnesium hydroxide
  4. Aluminum hydroxide

Antacids

Sodium bicarbonate [NaHCO3]

- Reacts rapidly with hydrochloric acid (HCL) to produce carbon dioxide and sodium chloride.

1. Formation of carbon dioxide results in gastric distention and belching.

2. **Unreacted alkali** is readily absorbed, potentially causing metabolic alkalosis when given in high doses or to patients with renal insufficiency.

3. Sodium chloride absorption may exacerbate fluid ret in patients with heart failure, hypertension, and rena insufficiency.

Antacids

Calcium carbonate

- is less soluble and reacts more slowly than sodium bicarbonate with HCl to form carbon dioxide and calcium chloride ($CaCl_2$).

- Like sodium bicarbonate, calcium carbonate may cause belching or metabolic alkalosis.

Antacids

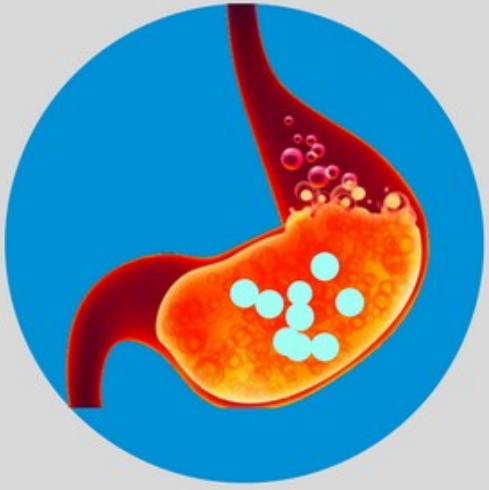
Magnesium hydroxide or **aluminum hydroxide**

- React slowly with HCl to form magnesium chl

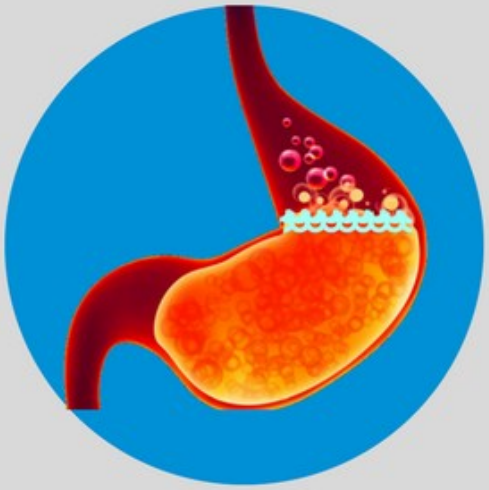
aluminum chloride and water.

- Because no gas is generated, belching does n
- 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 branded formulations (eg, Gelusil, Maalox, Mylanta) 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.

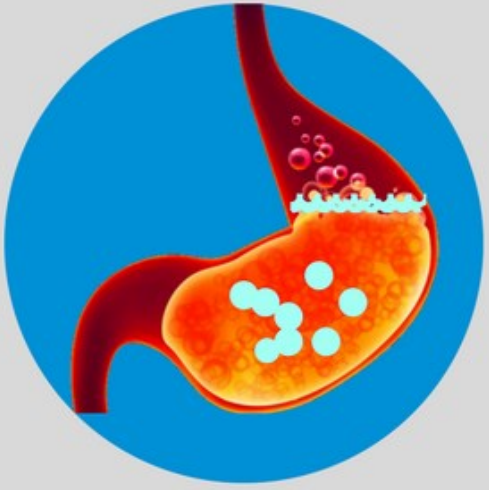
Alginic acid/antacid



Antacids work by counteracting, or neutralising, any excess stomach acid



Alginates form a 'raft' that floats on top of stomach contents



Combo products contain an antacid & a raft-forming alginate

H2- receptor antagonists

- Four H2 antagonists are in clinical use: **cimetidine, ranitidine, famotidine,** and **nizatidine**.
- From their introduction in the 1970s 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 proton pump inhibitors, the use of prescription H2 blockers has declined markedly.
- However, the over-the-counter preparations of the H2 antagonists are heavily used by the public.

H2- receptor antagonists

Adverse effects and drug interactions:

- In general, the H2 antagonists are well tolerated.
- Cimetidine inhibits several cytochrome P450 isoenzymes and can interfere with the metabolism of many other drugs.
- Cimetidine acts as a nonsteroidal antiandrogen and prolactin-stimulating effects.
- All H2 antagonists may reduce the efficacy of drugs that require an acidic environment for absorption, such as ketoconazole.

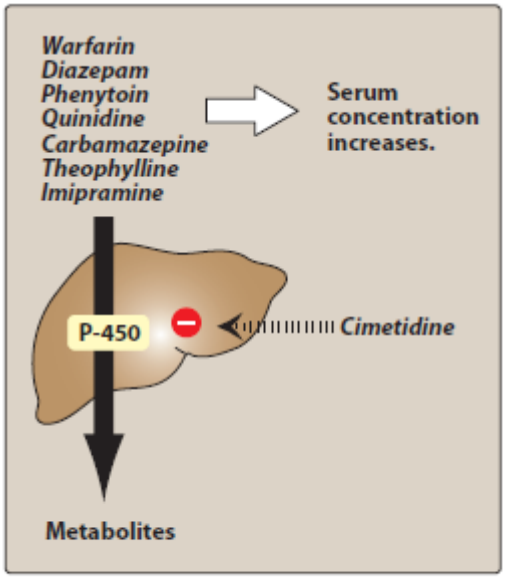


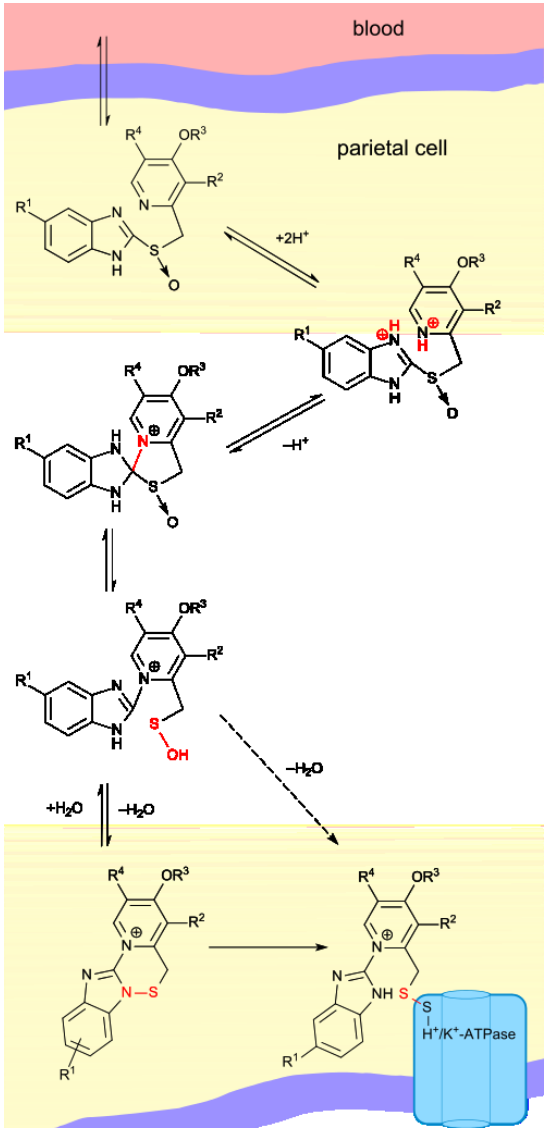
Figure 31.5
Drug interactions with *cimetidine*.

Proton Pump Inhibitors

- Since their introduction in the late 1980s, these efficacious acid inhibitory agents have assumed the major role for the treatment of acid-peptic disorders.
- Six proton pump inhibitors are available for clinical use: **omeprazole, esomeprazole, lansoprazole, dexlansoprazole, rabeprazole,** and **pantoprazole.**
- All are available in oral formulations. Esomeprazole and pantoprazole are also available in intravenous formulations.

Proton Pump Inhibitors

- Proton pump inhibitors are administered as inactive prodrugs.
- Oral formulations of these drugs are enteric coated to prevent acid inactivation in the stomach.
- PPIs are lipophilic weak bases that diffuse into the parietal cell, where they become protonated and concentrated more than 1000-fold. There they undergo conversion to compounds that irreversibly inactivate the parietal cell H+/K+ ATPase, the transporter that is primarily responsible for producing stomach acid.



Proton Pump Inhibitors

- All of these agents are effective orally.
- For maximum effect, PPIs should be taken 30 to 60 minutes before breakfast or the largest meal of the day. so that the peak serum concentration coincides with the maximal activity of proton pump secretion.
  - In a fasting state, only 10% of proton pumps are actively secreting acid and susceptible to inhibition.

- **Dexlansoprazole** has a dual delayed release formulation and can be taken without regard to food.

Proton Pump Inhibitors

- 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.

Proton Pump Inhibitors

- **Adverse effects and drug interactions**:
- Adverse effects occur infrequently and include diarrhea, abdominal pain, and headache.
- Proton pump inhibitors may decrease the oral bioavailability of vitamin B12 and certain drugs that require acidity for their gastrointestinal absorption (eg, digoxin, ketoconazole).

Proton Pump Inhibitors

- **Adverse effects and drug interactions**:
- The FDA has issued a warning about a potentially important adverse interaction between clopidogrel and PPIs.
  - Clopidogrel is a prodrug that requires activation by the hepatic P450 CYP2C19 isoenzyme.
  - PPIs such as omeprazole and esomeprazole inhibit CYP2C19, resulting in significantly reduced antiplatelet activity of clopidogrel. Other PPIs (dexlansoprazole, lansoprazole, pantoprazole, and rabeprazole) do not affect CYP2C19 to this extent.
  - Clopidogrel carries a boxed warning that **concomitant use with omeprazole or esomeprazole should be avoided**.

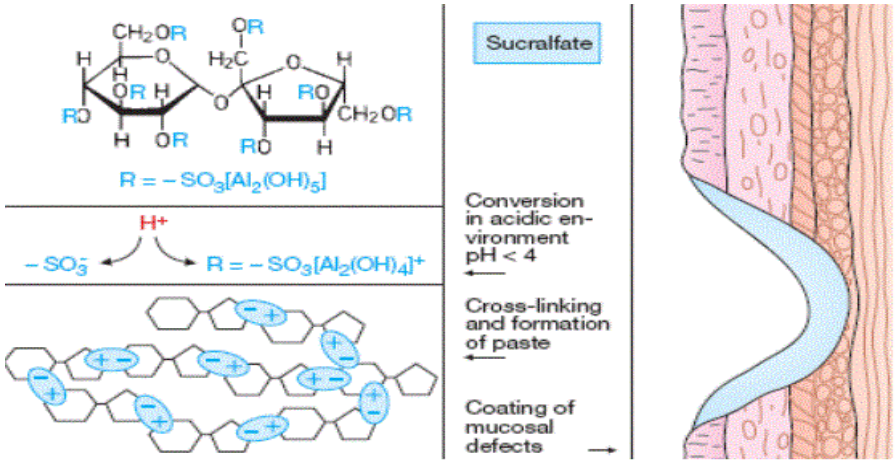
Mucosal Protective Agents

1. Sucralfate
2. Misoprostol
3. Bismuth compounds

Sucralfate

- **Sucralfate** is a salt of sucrose complexed to sulfated aluminum hydroxide.

- It polymerizes in the acid environment of the stomach.
- By forming complex gels with epithelial cells, sucralfate creates a physical barrier that protects the ulcer from pepsin and acid, allowing the ulcer to heal.



Sucralfate mechanism of action

Sucralfate

- Sucralfate must be taken 4 times daily on an empty stomach (at least 1 hour before meals).
- Because it requires an acidic pH for activation, *sucralfate* should not be administered with PPIs, H2 antagonists, or antacids.

- Sucralfate is too insoluble to have significant systemic effects when taken by the oral route; toxicity is very low.

  - Limitations of sucralfate include:
    - the need for multiple daily dosing
    - large tablet size
    - interaction with a number of other medications (eg, digoxin and fluoroquinolones).

Prostaglandin analog Misoprostol

- Prostaglandin E, produced by the gastric mucosa, inhibits secretion of acid and stimulates secretion of mucus and bicarbonate (cytoprotective effect).
- An analog of PGE1, **misoprostol** increases mucosal protection and inhibits acid secretion.

- Prophylactic use of misoprostol is considered in patients who are taking NSAIDs and are at moderate to high risk of NSAID-induced ulcers, such as elderly patients and those with previous ulcers (PPIs are preferred agents for the prevention of NSAID-induced ulcers).
- Misoprostol is contraindicated in pregnancy, since it can stimulate uterine contractions and cause miscarriage.
- Dose-related diarrhea and nausea are the most common adverse effects and limit the use of this agent.

Bismuth Compounds

- Two bismuth compounds are available:
  1. **Bismuth subsalicylate**
  2. **Bismuth subcitrate potassium.**

- Bismuth subsalicylate undergoes rapid dissociation within the stomach, allowing absorption of salicylate.

- Over 99% of the bismuth appears in the stool.

Bismuth Compounds

- The precise mechanisms of action of bismuth are unknown.

1. Bismuth coats ulcers and erosions, creating a protective layer against acid and pepsin.
2. It also stimulate prostaglandin, mucus, and bicarbonate secretion.
3. Bismuth subsalicylate reduces stool frequency and liquidity in acute infectious diarrhea.
4. Bismuth has direct antimicrobial effects and binds enterotoxins, accounting for its benefit in preventing and treating traveler's diarrhea.
5. Bismuth compounds have direct antimicrobial activity against *H pylori.*

Bismuth Compounds

Adverse Effects

- All bismuth formulations have excellent safety profiles.

1. Bismuth causes **harmless blackening of the stool**, which may be confused with gastrointestinal bleeding.
2. **Liquid** formulations may cause **harmless darkening of the tongue.**

Antibiotics

- Chronic infection with *H pylori* is present in most patients with recurrent non-NSAID-induced peptic ulcers.
- Eradication of this organism greatly reduces the rate of recurrence of ulcer in these patients.

- One regimen of choice "**triple therapy**" consists of:

1. A proton pump inhibitor
2. A course of clarithromycin
3. A course of amoxicillin (or metronidazole in patients with penicillin allergy) twice daily for 14 days.

- Bismuth-based **quadruple therapies** are commonly used as second-line therapies (PPI+ bismuth subsalicylate or subcitrate+ tetracyclin+ metronidazole)

Three-drug regimen

Table 18–2

Drug Regimens to Eradicate *Helicobacter pylori*[a,b]

Treatment Regimen	Cure Rates[b]
First Line: Three Drugs[c]	
Clarithromycin 500 mg + metronidazole 500 mg + omeprazole 20 mg, each given twice daily	Good to excellent
Clarithromycin 500 mg + amoxicillin 1 g + lansoprazole 30 mg, each given twice daily	Good to excellent

- Amoxicillin should not be used in penicillin-allergic patients
- Metronidazole should be avoided if alcohol is going to be consumed (disulfiram-like reaction).
- A single daily PPI dose is less effective than twice-daily dosing when used in a triple-drug regimen.
- Substitution of one PPI for another is acceptable and does not affect eradication rates.

Four-drug regimen

- Bismuth-based four-drug regimens have clinical cure rates similar to three-drug PPI-based regimens.
- Disadvantages of bismuth-based regimens include frequency of administration (four times a day), risk for salicylate toxicity in renal impairment, and bothersome side effects (eg, stool and tongue discoloration, constipation, nausea, vomiting).
- Therefore, bismuth-based quadruple therapy is usually considered second-line treatment.

First Line: Four Drugs	
Helidac™ (bismuth subsalicylate 525 mg + metronidazole 250 mg + tetracycline 500 mg, each given four times a day) + ranitidine 150 mg twice daily[c]	Good
Bismuth subsalicylate 525 mg four times a day + metronidazole 250 mg four times a day + tetracycline 500 mg four times a day + PPI twice daily OR ranitidine 150 mg twice daily[d,e]	Good
Pylera™ (bismuth subcitrate potassium 140 mg + metronidazole 125 mg + tetracycline 125 mg) three capsules twice daily + omeprazole 20 mg twice daily × 10 days	Good to excellent

Questions??