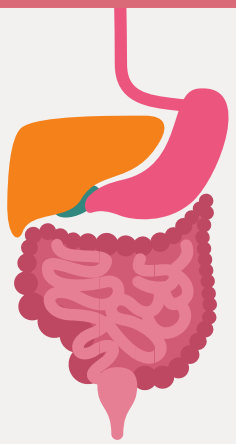
Drugs used in peptic ulcer



Objectives:

- Classify the main different classes of hypo-secretory drugs used for treating peptic ulcer.
- Know the characteristic pharmacokinetics, pharmacodynamics and side effects of proton pump inhibitors, and H2 receptor blockers.
- Know the cyto-protective drugs mainly misoprostol and its use in NSAIDs-induced peptic ulcer.
- Identify different antacids that are used to relief pain of peptic ulcer.

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Drugs names | Doctors notes | Important | Extra

« **باذلًا وسعي** في استنقاذها من الهلاك والمرض، والألم والقلق »

To understand better

Peptic ulcer

It is a localized lesion of the mucous membrane of the stomach (gastric ulcer) or duodenum (duodenal ulcer), typically extending through the muscularis mucosa.

Etiology

Helicobacter pylori is the major etiological factor in peptic ulcer disease (**PUD**).

Pathophysiology

Imbalance between **aggressive factors** (acid & pepsin) and **defensive factors** (e.g. prostaglandins, mucus & bicarbonate layer). However, nowadays, it seems that ***H. pylori*** theory is very important.

HCl & pepsin → destroy gastric and duodenal mucosa

Mucus and bicarbonate → Protect mucosa

Prostaglandins (PG**E**$_2$ & PG**I**$_2$) → Protect mucosa by:

Inhibiting acid secretion, increase mucus & bicarbonate production and enhance mucosal blood flow.

Risk factors

- *H. pylori* infection
- Alcohol
- Smoking
- Caffeine
- Genetic factors
- Diet
- Hypersecretory states (**Zollinger Ellison syndrome**)
- Drugs (e.g. NSAIDs)

Gastric secretions

Parietal cells:	**Chief cells:**	**Mucus secreting cells:**
HCl & intrinsic factor	Pepsinogens	Mucus, Bicarbonate

Regulation of gastric secretions

Parietal cells secrete acid in response to:

Histamine (local hormone) → H_2 receptor.

Gastrin (hormone): CCK_2 receptors.

Ach (neurotransmitter): M_3 receptors.

Proton pump (H^+/ K^+ ATPase).

Treatment of peptic ulcer

Treatment of peptic ulcer

- **Eradication of H. pylori infections**
  - combination of **metronidazole**/ **clarithromycin** and PPIs
- **Hyposecretory drugs**
  - Proton pump inhibitors
  - H_2 receptor blockers
  - Antimuscarinic drugs
  - Decrease gastric acid secretion → Promote healing & relieve pain.
- **Mucosal cytoprotective agents**
  - Prostaglandin analogues
- **Neutralizing agents (antacids)**
  - Used to relief pain, not a treatment.

Hypo-secretory drugs

Another helpful diagram-1

Another helpful diagram-2

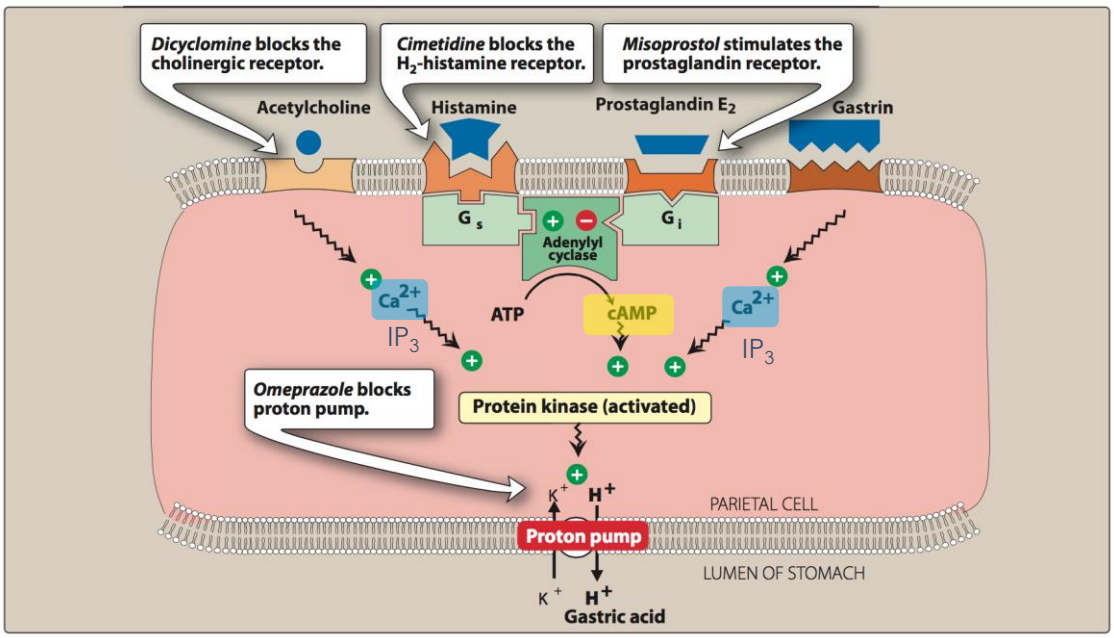


Figure 28.4
Effects of acetylcholine, histamine, prostaglandin E_2, and gastrin on gastric acid secretion by the parietal cells of stomach. G_s and G_i are membrane proteins that mediate the stimulatory or inhibitory effect of receptor coupling to adenylyl cyclase.

Note: Histamine binding causes activation of **adenylyl cyclase**, whereas binding of prostaglandin E_2 inhibits this enzyme. Gastrin and acetylcholine act by inducing an increase in intracellular **Ca^{2+}** levels.

Hypo-secretory drugs

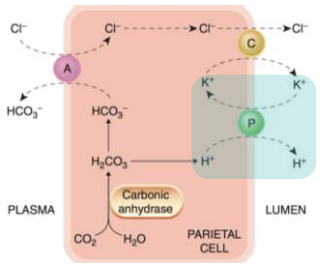
Proton Pump Inhibitors (PPIs)

Drug

Omeprazole, Lansoprazole, Pantoprazole, Rabeprazole

Mech. of action

- Irreversible inhibition of **proton pump (H^+/ K^+ ATPase)** (a reactive thiophilic sulfenamide cation, forms a covalent disulfide bond with the H^+/K^+-ATPase, irreversibly inactivating the enzyme.)
- → that is responsible for **final step** in gastric acid secretion from the parietal cell.



P.D

- They are the most potent inhibitors of acid secretion available today.
- Produce marked inhibition of basal (released without meal) & meal stimulated-acid secretion (90-98%). → Reduce **pepsin** activity.
- Reduce the risk of bleeding from an ulcer caused by aspirin and other NSAIDs.
- Promote mucosal healing & decrease pain → Proton pump inhibitors heal ulcers **faster than** H_2 blockers, and have ***H. pylori* inhibitory properties**.

P.K

- Orally, rapidly absorbed from the intestine.
- Pro-drug, They are activated inside the **acidic** medium of parietal cell canaliculi.
- At **neutral** pH, PPIs are inactivated. → Should **not** combined with drugs that decrease the acidity (increase stomach's pH): H_2 blockers or antacids. → because the H_2 antagonists will reduce the activity of the proton pump, and PPIs require active pumps to be effective.
- Given as **enteric coated formulations** (unstable in acidic medium in stomach).

→ The coating is removed in the **alkaline duodenum**, and the prodrug, a weak base, is absorbed and transported to the parietal cell canaliculus. There, it is converted to the **active form**, which reacts with a cysteine residue of the H+/K+-ATPase forming a stable covalent bond.

- Bioavailability is **reduced** by food.
- Given one half to one hour before the meal.
- Once daily dose is sufficient
- Metabolized in the liver by **Cyt-P450**.
- Dose reduction is required in severe **liver failure**.
- Long duration of action (>12-24h)

Uses

- Eradication of H. pylori (combined with antimicrobial drugs).
- **Resistant severe** peptic ulcer (4-8 weeks). + Stress ulcer.
- Reflux esophagitis.
- Hypersecretory conditions as Zollinger Ellison syndrome* and gastrinoma → (**First choice**). ▶ 1:41 min

ADRs

- CNS: Headache.
- Achlorhydria. → No HCl at all in the stomach.
- Hypergastrinaemia. → bc Gastrin levels are regulated by intragastric acidity (high HCl = inhibit gastrin secretion).
- Increased bacterial flora. → Gastric acid is an important barrier to colonization and infection of the stomach and intestine from ingested bacteria.
- Gastric mucosal hyperplasia.
- GIT: Diarrhea & abdominal pain.
- increased risk of community-acquired respiratory infections & nosocomial pneumonia.

Helpful pic

- Long term use (>1 year): Vitamin B_{12} deficiency (because acid is required for its absorption in a complex with intrinsic factor), Increased risk of **hip fractures** (decrease Ca^{2+} absorption).

Hypo-secretory drugs

H_2 receptor blockers

Drug

Cimetidine, Ranitidine, Famotidine, Nizatidine

MOA

- **Reversibly** and **competitively** block **H_2 receptors** on the parietal cells.

P.K

- Good oral absorption
- Given before meals.
- Duration of action (4-12 h).
- Excreted mainly in urine.
- Metabolized by liver.
- Exposed to **first pass metabolism** (except nizatidine that has the greatest bioavailability)
- **Famotidine** is the most potent drug.

P.D

- Pharmacological actions:
- Reduce **basal** and food stimulated-acid secretion.
- **Block 90% of nocturnal acid secretion** (which depend largely on histamine) & 60-70% of total 24 hr acid secretion. Therefore, it is better to be given before night sleep.
- Reduce pepsin activity.
- Promote mucosal healing & decrease pain.

Uses

- GERD (heartburn/ dyspepsia).
- Acute ulcer healing in moderate cases:
  - Duodenal Ulcer (6-8 weeks).
  - Benign gastric ulcer (8-12 weeks).
- Pre-anesthetic medication (to prevent aspiration pneumonitis).
- Prevention of bleeding from stress-related gastritis.
- **Post**–ulcer healing maintenance therapy.

ADRs

- GIT disturbances: Nausea & vomiting.
- CNS effects: **Headache**
- Elderly: confusion, hepatic dysfunction, renal dysfunction. → Precautions: Dose reduction of H_2 RAs in **severe renal** or **hepatic failure and elderly**.
- Bradycardia and hypotension (rapid **I.V.**) → due to blockade of cardiac H_2 R.
- **CYT-P450 inhibition** (Only **Cimetidine**) decrease metabolism of **warfarin**, **phenytoin**, **benzodiazepines**. → thus potentiate the action → Pic explains
- Endocrine effects (Only **Cimetidine**):
  - Galactorrhea (Hyperprolactinemia) → Infertility in female.
  - **Antiandrogenic actions** (gynecomasteia – impotence) due to inhibition of **dihydrotestosterone** binding to androgen receptors.

precaution

- Although there are no known harmful effects on the fetus, H_2 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. (Pregnant & breast feeding women)
- Liver disease.

Hypo-secretory drugs

	Cimetidine	Rantidine	Famotidine	Nizatidine
Efficacy	+++	+++	+++	+++
Potency	+	++	+++	++
Dose	400 mg bid	150 mg bid	20 mg bid	150 mg bid
Rout	PO, IV	PO, IV	PO, IV	PO, IV
$T_{1\backslash 2}$	Short (2h)	Longer (3h)	Longer (3h)	Shortest (1h)
Duration	5-6 h	10 h	12 h	11 h
CYT P 450	++	-	-	-
Antiandrogenic	++	-	-	-
Drug ineraction	Many	No	No	No

What is the difference between the efficacy & potency?
- Efficacy = All the drugs are effective in reducing HCl.
- Potency = Depends on one thing, the conc. of the drug
  → The lowest conc. = The highest effect. → e.g. Famotidine.

Prostaglandin analogues (PGE1) → Misoprostol

MOA
- **Lowers HCl secretion**.
- Increase the protective measures → (↑ mucous / bicarbonate & gastric mucosal blood flow).
- PGE & PGI → have cyto-protective mechanism on the stomach.

P.K
- Orally, must be taken 3-4 times\day.

Uses
- **Used for NSAIDs-induced peptic ulcer**. → bc non-specific NSAIDs inhibit prostaglandins. that's why nowadays they produce selective COX-2 inhibitors.

ADRs
- **Abdominal cramps**; **diarrhea**. → prostaglandins increase GIT motility.
- **Uterine contraction** (dysmenorrhea or abortion), dislodging of the fetus
- Vaginal bleeding.

C.I
- Pregnancy.

Antacids

MOA

- These drugs are mainly **inorganic salts** e.g. $NaHCO_3$; $CaCO_3$; $Al(OH)_3$; $Mg(OH)_2$.
- Acts by **direct chemical neutralization of HCL** (No receptors action) and as a result may decrease pepsin activity → Because pepsin is inactive at a pH greater than 4.

P.K

- **All** antacids ↓ absorption of some drugs as tetracycline, fluoroquinolones, iron.

Use

- Used to relief pain of peptic ulcer & for dyspepsia.

ADRs

- **$NaHCO_3$(sodium bicarbonate)**: Effective, but systemic alkalosis may occur, contraindicated in CVS patients.
- **$CaCO_3$ (Calcium carbonate)**: Milk alkali syndrome. (hypercalcemia, renal failure)
- **$Al(OH)_3$ (Aluminum hydroxide)**: **constipation**, Systemic phosphate depletion → The binding of phosphate by aluminum-containing antacids can lead to hypophosphatemia (weakness, malaise, anorexia)
- **$Mg(OH)_2$**: **Diarrhea**, Magnesium trisilicate-- slow-acting antacid.

→ so mixtures of latter two can, happily, be used to preserve normal bowel function

Quick summary

Treatment of peptic ulcer

H. pylori

Test for *H. pylori* prior to beginning therapy.

Complete *H. pylori* eradication is required to prevent relapse.

PUD* with *H. pylori* infections can be treated with triple therapy or quadrable therapy.

Acid reducing medications → in case of PUD without H pylori infections.

H2 receptor antagonist.

PPI's should be used for:

- **Acute** therapy only if H2RAs **fail** or cannot be used
- As part of treatment for *H. pylori*.

* Peptic ulcer disease

Summary-1

Treatment of peptic ulcer

1- Eradication of *H. pylori* infections. → Metronidazole + clarithromycin and PPIs.	**3-** Mucosal cytoprotective agents.
2- Hyposecretory drugs	**4-** Neutralizing agents (antacids)

Hyposecretory drugs

	Proton Pump Inhibitors (PPIs)	H_2 receptor blockers (H_2RAs)
Drug	Omeprazole, Lansoprazole, Pantoprazole, Rabeprazole	Cimetidine, Ranitidine, Famotidine, Nizatidine
MOA	Irreversible inhibition of proton pump (H^+/ K^+ ATPase).	Reversibly and competitively block H_2 receptors on the parietal cells.
P.D	- The most potent inhibitors of acid secretion. - Marked inhibition of basal & meal stimulated-acid secretion. - Reduce pepsin activity. - Promote mucosal healing & decrease pain.	- Reduce basal and food stimulated-acid secretion. - Block 90% of nocturnal acid secretion → better to be given before night sleep. - ↓ Pepsin activity. - Promote mucosal healing & decrease pain.
P.K	- Oral, rapidly absorbed from the intestine. - Activated inside acidic medium of parietal cell canaliculi → Inactive in neutral pH. - Not combined w\ H_2RAs or anacids. - Bioavailability is reduced by food. - Long duration of action. - Reduce dose with sever liver failer.	- Good oral absorption. - Giver before meals. - Metabolized by liver. - Exposed to 1st pass metabolism except Nizatidine (has the greatest bioavailability) - Famotidine is the most potent drug.
Uses	- **Eradication of *H. pylori***. - Resistant severe peptic ulcer. - Reflux esophagitis. - 1st choice with hypersecretory condition e.g. Zollinger Ellison syndrome and gastrinoma.	- GERD. - Acute ulcer healing in moderate cases - Pre-anesthetic medication (to prevent aspiration pneumonitis). - Prevention of bleeding from stress-related gastritis. - Post–ulcer healing maintenance therapy.

ADRs	- Headache.
	- Achlorhydria.
	- Diarrhea.
	- Hypergastrinaemia.
	- ↑ bacterial flora.
	- Risk of respiratory infection.
	- Long use: ↓ Vit.B12 , ↑ hip fracture.
		- Nausea & vomiting.
		- Headache & confusion.
		- Hepatic dysfunction & renal dysfunction → Elderly.
		- Bradycardia and hypotension (rapid I.V.).
		- Only Cimetidine ADRs:
		  - CYT-P450 inhibition.
		  - Galactorrhea.
		  - Antiandrogenic actions.

Summary-2

	Antacids	Prostaglandin analogues (PGE1) → Misoprostol
MOA	- They are mainly **inorganic salts** e.g. $NaHCO_3$; $CaCO_3$; $Al(OH)_3$; $Mg(OH)_2$. - Direct chemical neutralization of HCL and as a result may decrease pepsin activity.	- **Lowers HCL secretion.** - Increase the protective measures.
P.K	**All** antacids ↓ absorption of some drugs as tetracycline, fluoroquinolones, iron.	Orally, must be taken 3-4 times\day
Uses	Used to relief pain of peptic ulcer & for dyspepsia.	**Used for NSAIDS-induced peptic ulcer**.
ADRs	- **$NaHCO_3$**: Systemic alkalosis. - **$CaCO_3$**: milk alkali syndrome. (hypercalcemia, renal failure) - **$Al(OH)_3$**: constipation. - **$Mg(OH)_2$**: Diarrhea.	- Abdominal cramps; diarrhea - **Uterine contraction** (dysmenorrhea or abortion); vaginal bleeding.

Clinical use of agents affecting gastric acidity

- Histamine H_2 receptor antagonists (e.g. **ranitidine**):
  - *peptic ulcer*
  - *reflux oesophagitis.*
- Proton pump inhibitors (e.g. **omeprazole**, **lansoprasole**):
  - *peptic ulcer*
  - *reflux oesophagitis*
  - as one component of therapy for *Helicobacter pylori* infection
  - *Zollinger–Ellison syndrome* (a rare condition caused by gastrin-secreting tumours).
- Antacids (e.g. **magnesium trisilicate**, **aluminium hydroxide**, **alginates**):
  - *dyspepsia*
  - symptomatic relief in *peptic ulcer* or (alginate) *oesophageal reflux*.
- **Bismuth chelate**:
  - as one component of therapy for *H. pylori* infection.

MCQs

1- Patient has Gastrin-secreting tumor of the pancreas which one of the following is the proper treatment?
A- Cimetidine
B- Misoprostol
C- Omeprazole
D- $NaHCO_3$

2- Patient was prescribed a drug for heartburn, later he complained of sexual dysfunction. what was the drug?
A- Omeprazole
B- Cimetidine
C- Nizatidine
D- Famotidine

3- Medical student complained of stress related gastritis. Which one of the following drugs can be used to prevent bleeding?
A- Misoprostol
B- $CaCO_3$
C- Raprazole
D- Famotidine

4- Patient was taking medication for back pain for a long time, later he developed an epigastric pain, nausea and vomiting. Which one of the following is the underlying cause?
A- Inhibit synthesis of gastrin
B- Inhibit synthesis of leukotrienes.
C- Inhibit synthesis of prostaglandins
D- Inhibit synthesis of COX-2

5- Which one of the following inorganic salts may develop milk alkali syndrome?
A- $Mg(OH)_2$
B- $AL(OH)_3$
C- $NaHCO_3$
D- $CaCO_3$

6- Which inorganic salt can cause diarrhea?
A- $Mg(OH)_2$
B- $AL(OH)_3$
C- $NaHCO_3$
D- $CaCO_3$

Answers: 1-C 2-B 3-D 4-C 5-D 6-A

Thank you for checking our team!

Pharmacology 435

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Sources:

1. 435's slides.
2. Pharmacology (Lippincotts Illustrated Reviews Series), chapter 28, 5th edition.
3. Basic & Clinical Pharmacology by Katzung, chapter 62,12th edition.
4. Rang & Dale's pharmacology, chapter 29, 7th edition.