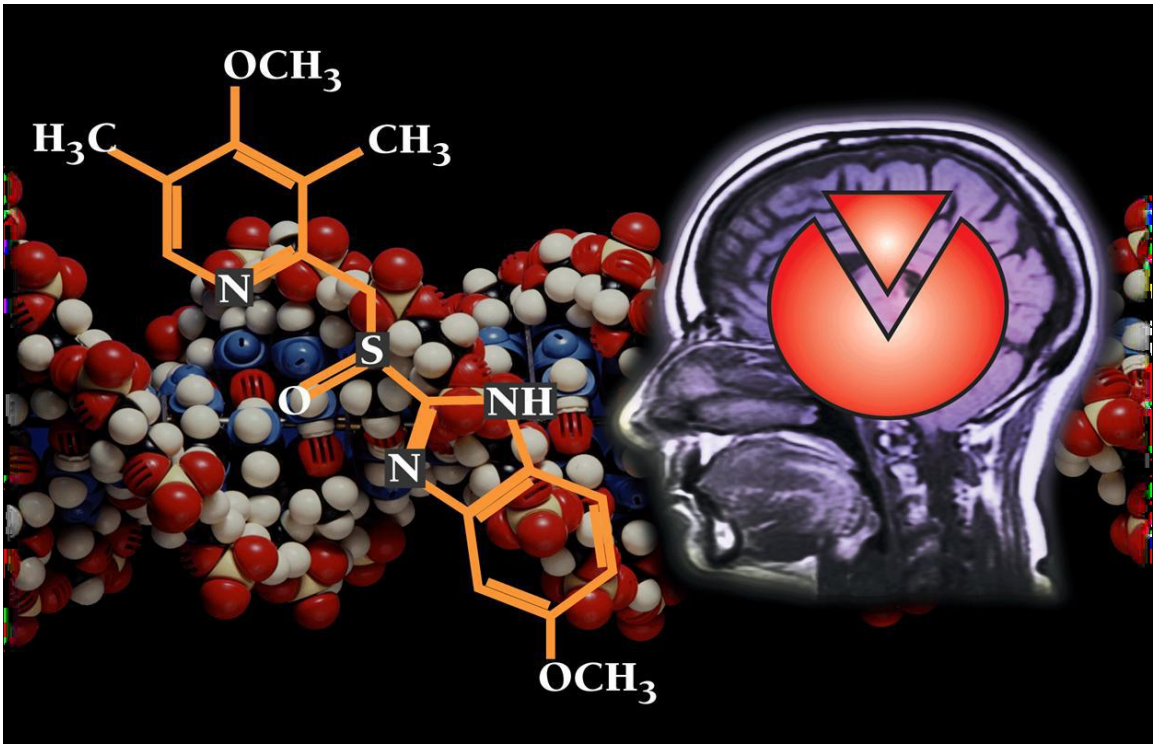
King Saud University
College Of Medicine
Pharmacology Team 430
GIT Block

Drugs used for peptic ulcer



Note: First three pages are for explanation only, and are not required from you in the exam.

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Definition:

(Classified as: peptic ulcer disease (gastric, duodenal) and gastro esophageal reflex disease or stress related ulcer).

Stress ulcers are single or multiple mucosal defects which can become complicated by upper gastrointestinal bleeding during the physiologic stress of serious illness. Ordinary peptic ulcers are found commonly in the gastric antrum and the duodenum whereas stress ulcers are found commonly in fundic mucosa and can be located anywhere within the stomach and proximal duodenum.

Note: In all these conditions, mucosal erosions or ulceration arise when the caustic effects of **aggressive factors (acid, pepsin, bile)** overwhelm the **defensive factors** of GI mucosa (**mucus & bicarbonate secretion, PGs, blood flow, regeneration).**

Etiology:

Smoking(related to peptic ulcers), Caffeine(related to esophageal reflux, causes dilation to the sphincters); Heredity; Diet; Hypersecretory states; H. pylori infection; alcohols; Drugs, like NSAID (aspirin, ibuprofen , naproxen ketoprofen), bisphosphonates (used to treat osteoporosis). ulcers.

notes: acetaminophen(paracetamol) doesn't cause peptic.
-Over 90% of **peptic ulcers** are caused by: infection with the bacterium ***Helicobacter pylori*** or by use of Nonsteroidal anti-inflammatory drugs (NSAIDs).

Pathophysiology: (see figure Next page): Simply and as what mentioned above it is imbalance between Aggressive factors (Acid & Pepsin) and Defensive Factors (e.g. Prostaglandins), **However, nowadays, it seems that H. pylori theory is very important.**

Symptoms : Nausea –Vomiting –Anorexia - Upper abdominal pain - Weight loss- Heart burn.

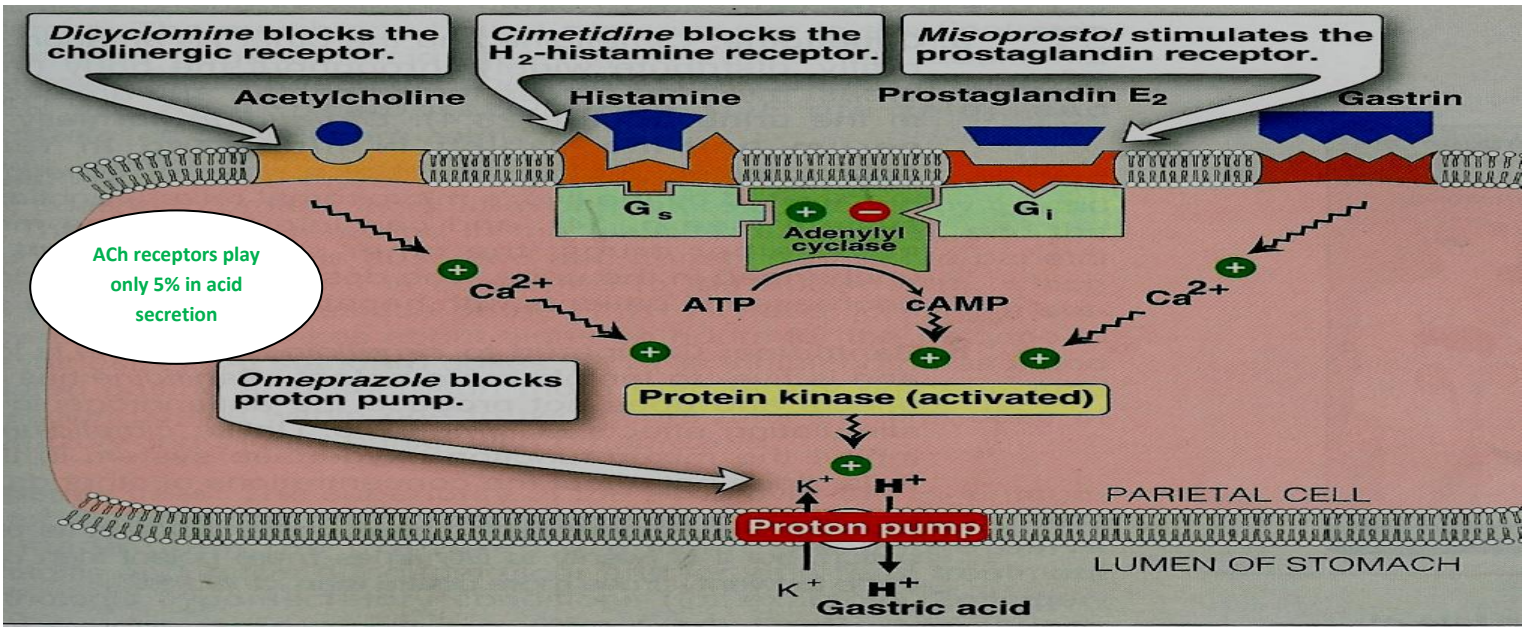
Complications: Gastrointestinal hemorrhage - Chronic iron deficiency anemia- Perforation

Treatment

Objectives are (Relieve pain; healing of ulcer ; prevention of further ulcer recurring ; prevention of complications)

How the above objectives could be accomplished?

1) Inhibiting the aggressive factors e.g Acid and pepsin
2) Enhancing mucosal resistance
3) Eradication of H.pylori **(Best).**



Gastric acid secretion by parietal cells of the gastric mucosa is stimulated by **acetylcholine, histamine, and gastrin .**The receptor-mediated binding of **acetylcholine, histamine, or gastrin** results in the activation of **protein kinases**, which in turn stimulates the **H+/K+ adenosine triphosphatase** (ATPase) proton pump to secrete **hydrogen ions** in exchange **for K+** into the lumen of the stomach. A Cl- channel couples chloride efflux to the release of H+. In contrast, receptor binding of **prostaglandin E2 and somatostatin** diminish gastric acid production. [Note: Histamine binding causes activation of adenylyl cyclase, whereas binding of prostaglandin E2 inhibits this enzyme. Gastrin and acetylcholine act by inducing an increase in intracellular calcium levels.

In short: The parietal cell contains receptors of: **gastrin , histamine (H2) , and acetylcholine** (muscarinic, M3) and they all cause secretion of HCL, and **prostaglandin E2 and somatostatin** decrease the secretions.

Classification of Drugs used in the treatment of peptic ulcers

- antacids
  e.g. Al/Mg hydroxides
- anti-secretory drugs
  - H2-antagonist
    e.g. ranitidine
  - proton pump inhibitors
    e.g. omeprazole

Drug treatment of peptic ulcer

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I. Gastric hyposecretory drugs (reduce gastric acidity)

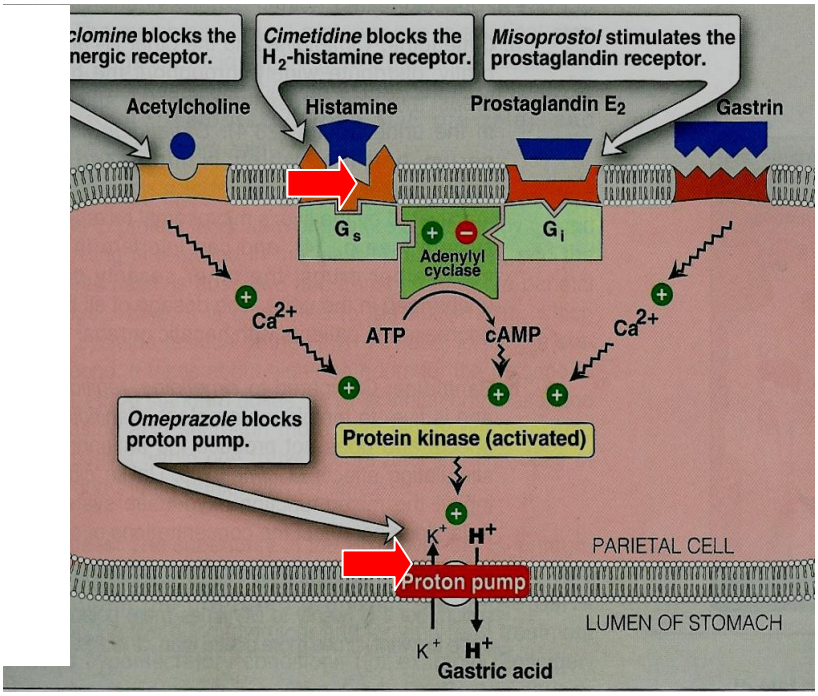
- **H2 receptor blockers**
- **Antimuscarinic drugs**
- **proton pump inhibitors**

II. Mucosal cytoprotective agents

- **Sucralfate**
- **Prostaglandin analogues**
- **Colloidal bismuth**

III. Eradication of H. pylori infections

IV. Neutralizing agents (antacids).



1-Antacids

These drugs are mainly inorganic salts (e.g.: $NaHCO_3$; $Ca\ CO_3$; most commonly used $Al\ (OH)_3$; $Mg\ (OH)_2$)

OH "hydroxyl group" reacts with acids and neutralize it, forming a salt and water.

Mechanism of Action:

(Antagonize acid; Also, Indirectly **may decrease pepsin activity, how? Pepsin becomes inactive at pH greater than 4)**

Note: they are used in **symptomatic** relief of peptic ulcer disease and GERD.

What are their side effects ?

constipation (from Al), diarrhea (from Mg), hypophosphatemia…others

note: preparations that combine both Al and Mg hydroxides are used as their actions will cancel each other.

What is the milk-alkali syndrome?

hypercalcemia caused by repeated ingestion of calcium and absorbable alkali (such as calcium carbonate, or milk and sodium bicarbonate). If untreated, milk-alkali syndrome may lead to metastatic calcification and renal failure.

Why their uses have been declined?

Because now we have stronger agents.

2-histamine (H_2 –receptor antagonists)

(considered the most important discovery in the seventies).

Examples:

Cimetidine (prototype)
most clinically used : Ranitidine (Zantac); **Famotidine** (most potent) ; **Nizatidine**

MOA: They competitively **& reversibly** bind to H2-receptors on the parietal cells, thus decreasing the production of acid by these cells.

Highly selective on H2 receptors.

Note: Circled in red are the most important points

	CIMETIDINE	RANITIDINE	FAMOTIDINE	NIZATIDINE
Efficacy	+++	++ +	+++	+++
Potency	+	++	+++	++
Dose	400 mg bid	150 mg bid	20mg bid	150 mg bid
Route	orally, IV	orally, IV	orally, IV	orally
T 1/2	short (2 h)	longer (3h)	longer (3h)	shortest (1
Duration	5-6 h	10 h	12 h	11 h
CYT P 450	++	-	-	-
Antiandrogenic	++	-	-	-
Drug interactions	many	No	No	No

Potency VS efficacy (see table)

Remember: **Ranitidine** is more potent; 150 mg can give the therapeutic effect, compared to 400 mg for **cimetidine.**

Pharmacokinetics

- Good & rapid oral absorption
- Plasma half life (1-4 hr).
- Duration (4-12 h) , given twice a day
- First pass metabolism (50%, **Except Nizatidine 100 % bioavailability).**
- Given before meals (all PU drugs are given on empty stomach)
- Clearance by hepatic metabolism, glomerular filtration & renal tubular secretion.
- Dose reduction is required in patients with moderate-severe renal (or severe hepatic) insufficiency.
- 50% clearance decline in elderly
- Cross placenta & excreted in milk.

Drug interactions:

- **Cytochrome P450 inhibition (**mostly with **cimetidine(potent inhibitor)** , then ranitidine) It decreases metabolism & prolong $t_{1/2}$ of: **warfarin, phenytoin, theophylline.**
- H2 antagonists compete with **creatinine** & certain drug (procainamide; antiarrhythmic) for renal tubular secretion therefore it prolongs **their $t_{1/2}$**

Pharmacological actions:

1. Reduce basal & food-stimulated gastric acid secretion.
2. Reduce acid secretion stimulated by histamine, as well as by gastrin & cholinergic drugs.
3. Reduce pepsin activity.
4. 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 and it is not as potent as PPIs because of blocking only 60-70% of total acid secretion.

Adverse Effects:

"safe drug, adverse effects occur in less than 3% of patients"

1. CNS effects: Headache,confusion, hallucination & agitation due to IV H2 antagonist (more with cimetidine in ICU especially (elderly –renal or hepatic dysfunction)) but not with Ranitidine.

2. Endocrine effects (For Only Cimetidine)
   - × Increases in serum prolactin (Galactorrhea in women).
   - × Inhibits binding of dihydro-testosterone to androgen receptors (gynecomasteia –impotence).
3. All cross placenta & breast milk, should not be given in pregnancy unless it is necessary. ranitidine can be given to pregnant woman.
4. Inhbition of Cty p450 by Cimetidine. (potential toxicity from other drugs administered concomitantly).
5. Leukopenea and thrombocytobenia and headache with ranitidine(rare).
6. GIT disturbances (Nausea & Vomiting)
7. Bradycardia & hypotension (rapid I.V)

Note: 70% of drug is excreted in urine, so the dose must be decreased in patients with renal failure.

Clinical USES:

1. GERD (gastroesophageal reflux disease), (heartburn/ dyspepsia).
2. PUD(peptic ulcer disease): effective in nocturnal acid suppression & ulcer healing in moderate cases
3. Prevention of bleeding from stress-related gastritis.
4. Decrease the heartburn by NSAIDs.
5. Zollinger Ellison Syndrome (large doses).

3- Proton pump inhibitors

"Since their introduction in the late 1980s, these efficacious acid inhibitory agents are now among the most Widely prescribed drugs in acid-peptic disorders."

Examples: Omeprazole ; Lansoprazole ; Pentoprazole ; Raprazole

MOA :

- Irreversible inhibition of proton pump (H^+ / K^+ ATPase) that is responsible for final step in gastric acid secretion from the **parietal cells.**
- 24 hr inhibition of basal & meal stimulated-acid secretion (90-98%).

Why PPIs should not be used together with H_2-antagonists or antacids?

PPIs are prodrugs (need to be activated in the body). PPI are converted to their active form by protonation (the source of protons is the acid in the stomach). When using H2-antagonist or antacids, less acid will be available (which is the source of protons). PPIs will not be of any benefit. We will waste the drug (IPPs) in that case.

Efficacy & potency: more potent than H2-blockers

Clinical Uses:

1) Gastric and duodenal ulcer (H.pylori Eradication)
2) Zollinger–Ellison syndrome. (1st) ← **is a triad of gastric acid hypersecretion, severe peptic ulceration, non-beta cell islet tumor of pancreas (gastrinoma).**
3) GERD
4) NSAIDs associated ulcer
5) prevention of bleeding from stress-related gastritis.
6) PUD (4-8 weeks); faster & long- lasting ulcer relief.

Side Effects:

- Headache.
- Diarrhea.
- Nausea.
- decreased gastric acid secretion lead to hypergastrinemia (one of the body's mechanism in response to high pH (in the stomach) is increased release of gastrin in an attempt to lower the stomach pH).
- mucosal hyperplasia.

► **prolonged acid suppression leads to:**

- subnormal B12 levels (because acid is required for its absorption).
- risk of hip fracture if taking PPIs over a long period.(PPIs may reduce calcium absorption or inhibit osteoclast function).
- colonization & infection of the stomach & intestine from ingested bacteria; increased risk of both community-acquired respiratory infections & nosocomial pneumonia.

Note: Despite all the above PPIs are very save drugs, but not preferred to be used in long periods.

Pharmacokinetics

Note: They are taken In IV forms in patients with gastric bleeding.

- They are prodrugs.
- All are taken orally.
- Esomeprazole & pantoprazole are also available in IV formulation. Give to those who can't swallow because of bleeding.
- All are given as enteric coated tablets/ capsules –To protect them from destruction by acidity in gastric lumen
- They are rapidly absorbed from the intestine & converted to active form.
- PPIs have plasma half life of 1.5 h
- Long duration of action (> 12 h-24 h), because of the irreversible inactivation of the proton pump.
- Once daily dose is sufficient
- Bioavailability is reduced by food (50%).
- Given 1 h before meal; on empty stomach.
- Are metabolized in the liver by CytP450. So dose reduction is required in severe liver failure.
- They are more potent than H2 antagonists.

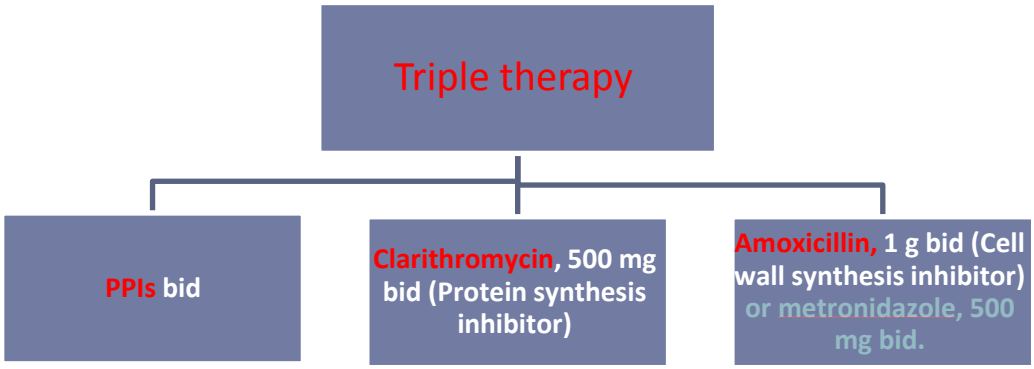
H2 Blockers	PPIs
block one of the 1st stimuli for acid production	block the final step in the pathway of acid secretion (greater suppression)
usually only work up to 12 hours.	work for a longer period of time; (up to 24 hr) & the effects may last up to 3 days.

How Gastrooesophageal Reflux could be managed?

- Decrease gastric acidity (**H2 blockers or PPIs**).
- Increase tone of LOS (lower esophageal sphincter) and increase gastric emptying by **Metoclopramide.**
- Avoid drugs or foods that trigger GERD. (caffeine, alcohol, smoking).
- Avoid sleeping after meal and try to use two to three pillows.

Eradication Of H. Pylori

- Is a bacteria that causes chronic inflammation of the inner lining of the stomach.
- Duodenal ulcer -Gastric ulcer.
- Produces enzymes (tissue damage).
- Risk factor for gastric cancer.
- Eradication is important to prevent recurrence of ulcer.
- The best treatment regimen: Triple therapy (10-14 days).



Note bid: twice daily, tid: three times daily

Summary:

- Most common cause (agent) in peptic ulcer H. Pylori infection. Others: smoking, caffeine, drugs…etc.
- Objective of treatment: (prevention of further ulcer recurring, Relieve pain; healing of ulcer).
- Best approach in treatment is the eradication of H. Pylori.
- Treatment available: antacids, H2-antagonist, and PPI.
- Antacids give symptomatic relief, Al and Mg hydroxides most commonly used.
- H2-antagonist: Ranitidine(more potent), cimetidine(enzyme inhibitor +anti-androgenic)
- All cross placenta.
- PPIs irreversibly inhibit proton pump (H/K ATPase).
- Do not use PPIs concomitantly with H2-antagonist.
- PPI are more potent than H2-antagonist.
- PPI side effects: diarrhea, nausea + hypergastrinemia + B12 deficiency + risk of hip fracture.
- PPIs are pro-drugs.
- One of the ways to manage Gastroesophageal reflux is to avoid sleeping after meal and try to use two to three pillows.
- Eradication of H. Pylori by triple therapy for (10-14) days. (chart above).
- Clinical uses of IPP include: Gastric and duodenal ulcer **(H.pylori Eradication),** Zolinger Elison syndrome. GERD, NSAIDs.
- Clinical uses of H2-antagonist: PUD (effective in nocturnal acid suppression), prevention of bleeding form stress-related gastritis.