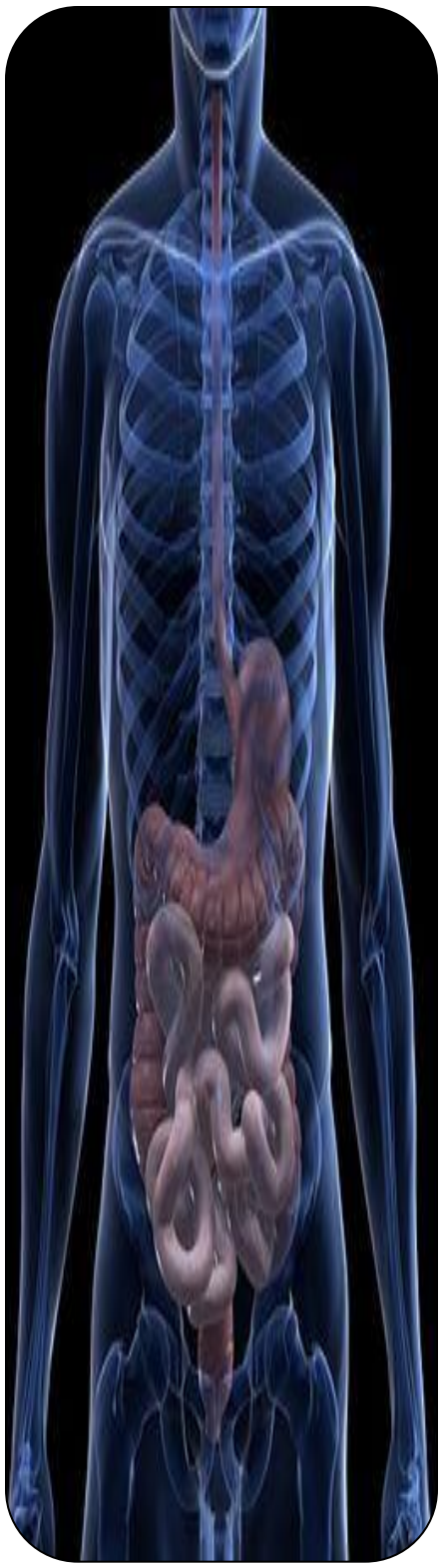

Pharmacology Team

Drugs Used For Peptic Ulcer

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Definition:

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

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

Etiology:

-Smoking(related to peptic ulcers)
-Caffeine(related to esophageal reflux, causes dilation to the sphincters)
-Heredity
- Diet
- Hypersecretory states
- **H. pylori infection (is the major etiological factor in PUD and requires treatment with antimicrobial agents)**
- alcohols
-Drugs, like NSAID (aspirin, ibuprofen , naproxen ketoprofen), bisphosphonates (used to treat osteoporosis) (because NSAID inhibit cox (cox change arachidonic acid to prostaglandins))

Pathophysiology:

Simply it is imbalance between Aggressive factors (Acid, Pepsin, bile) and Defensive Factors (e.g. mucus & bicarbonate secretion, PGs, blood flow, regeneration),
However, nowadays, it seems that H. pylori theory is very important.

Q/ What is the role of gastric emptying on the formation of ulcers?
Answer: If the gastric emptying is slow it causes gastric and esophageal ulcers, and if it is fast it causes duodenal ulcer.

Treatment:

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

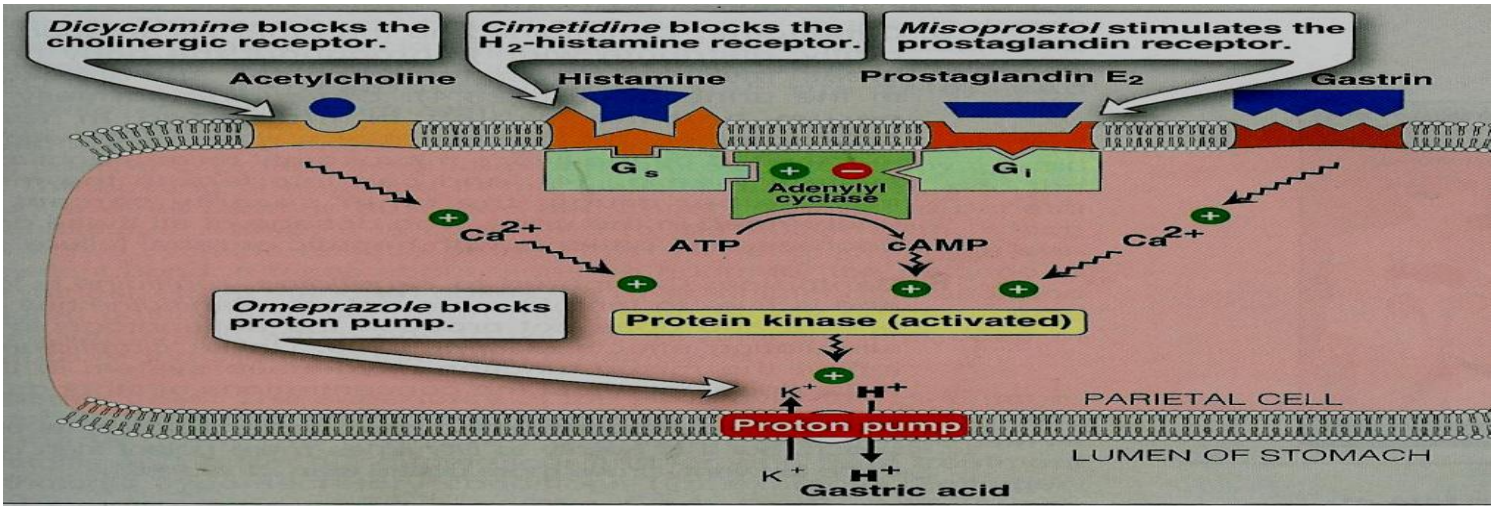
How could the above objectives be accomplished?

1) Inhibiting the aggressive factors e.g Acid and pepsin.
2) Enhancing mucosal resistance.

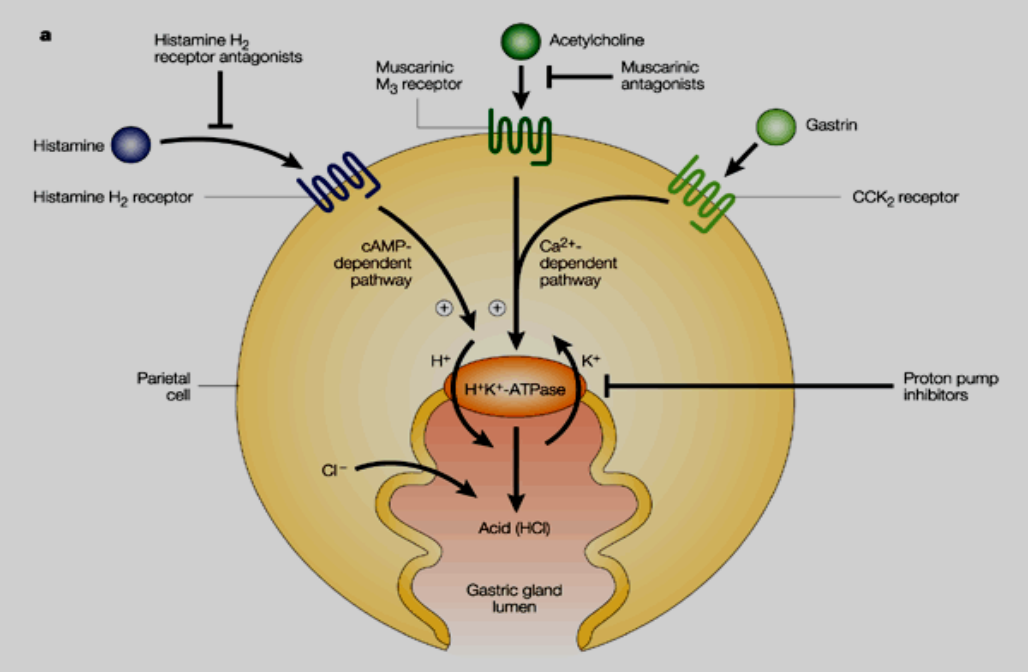
3) Eradication of H.pylori**(Best).**90%

Gastric secretions

1. HCl and intrinsic factor (Parietal cells).
2. Pepsinogens (Chief cells).
3. Mucus, bicarbonate (mucus-secreting cells).



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.
The final step before acid secretion is Proton pump (H+/ K+ ATPase)



Classification of drugs used in the treatment of peptic ulcers:

1- Antacids (e.g. Al/Mg hydroxides).
2- anti-secretory drugs:
a) H2- antagonist (e.g. ranitidine)
b) Proton pump inhibitors (e.g. omeprazole)
c) Antimuscarinic drugs

***Hyposecretory drugs decrease gastric acid secretion ➔Promote healing & relieve pain.**

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- H2-receptor antagonist:

(Considered the most important discovery in the seventies).

Examples: Cimetidine (prototype)**- Ranitidine -Famotidine - Nizatidine**

Most clinically used:Ranitidine (Zantac); **Famotidine** (most potent) ;**Nizatidine**.

MOA (Mechanism of action):

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

Cimetidine is one of the famous cytochrome P450 inhibitor "increase the half-life of others"

Could cause gynecomastia and impotence

Potency VS efficacy (see table)

Potency is the relationship between the dose of a drug and the therapeutic effect. It refers to the drug's strength. A drug is considered potent when a small amount of the drug achieves the intended effect. Efficacy is the ability of a drug to produce the desired therapeutic effect. Efficacy means that the drug is effective. When comparing two drugs that work equally, the one with the lower dose has a higher potency. They have equal efficacy.

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

Doctor didn't mention that the ranitidine is CYT P 450 inhibitor, but it is.

Drug interactions:

- **Cytochrome P450 inhibition (**mostly with **cimetidine(potent inhibitor)** , then ranitidine) It decreases metabolism & prolong t1/2 of: **warfarin, phenytoin, theophylline.**
- H2 antagonists compete with **creatinine**& certain drug (procainamide; antiarrhythmic) for renal tubular secretion therefore it prolongs **their t1/2**

Pharmacokinetics:

-Good oral absorption
-Given before meals.
-Famotidine is the most potent drug.
-Exposed to first pass metabolism (except nizatidine that has 100 % bioavailability).
-Duration of action (4-12 h).
-Metabolized by liver.
-Excreted mainly in urine.
-Cross placenta & excreted in milk (should not be given in pregnancy unless it is necessary)

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.(because H2 blockers decrease the acidity and pepsin need acid to be activated)

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**.

5. Promote mucosal healing & decrease pain

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 (Antiandrogenic actions) (gynecomasteia –impotence).

3. All cross placenta & breast milk, should not be given in pregnancy unless it is necessary. (not teratogenic) ranitidine can be given to pregnant woman.

4. Inhbition of CYT- P450 only Cimetidine. (potential toxicity from other drugs administered concomitantly). (decrease metabolism of warfarin, phenytoin, benzodiazepines)

5. Leukopenea and thrombocytobenia and headache with ranitidine(rare).

6.GIT disturbances (Nausea & Vomiting)

7. Bradycardia and hypotension (rapid I.V.)

Precautions : Dose reduction of H2 RAs in severe renal or hepatic failure and elderly.

Clinical USES:

1. GERD (gastroesophageal reflux disease), (heartburn/ dyspepsia).
2. PUD (peptic ulcer disease): effective in nocturnal acid suppression & ulcer healing in moderate cases (not use it in sever)

Acute ulcer healing: -Duodenal Ulcer (6-8 weeks)
-Benign gastric ulcer (8-12 weeks)

3.Post–ulcer healing maintenance therapy.
4.Pre-anesthetic medication (to prevent aspiration pneumonitis).
5.Zollinger Ellison Syndrome (large doses)
6. Prevention of bleeding from stress-related gastritis.
7. Decrease the heartburn by NSAIDs.

3- Proton pump inhibitors

Examples: Omeprazole ;Lansoprazole ; Pentoprazole ; Raprazole.

MOA (mechanism of action):

-Irreversible inhibition of proton pump (H+/ K+ ATPase) that is responsible for final step in gastric acid secretion from the **parietal cells.**

- 24 hrs. inhibition of basal & meal stimulated-acid secretion (90-98%).

Why PPIs should not be used together with H2-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.

Pharmacodynamics:
-Produce marked inhibition of basal and stimulated-acid secretion.
-They are the most potent inhibitors of acid secretion available today

Clinical Uses:

1) Gastric and duodenal ulcer (H.pylori Eradication) **(combined with antimicrobial drugs).**
2) Zollinger–Ellison syndrome and gastrinoma (First choice).
3) GERD
4) NSAIDs associated ulcer
5) Resistant severe peptic ulcer (4-8 weeks) >>used for acute therapy only if H2RAs fail or cannot be used

Gastrin-secreting tumor of the pancreas. non-beta cell islet tumor of pancreas (gastrinoma)
Gastrin produce:
-Parietal cell hyperplasia (trophic factor).
-Excessive gastric acid production

Pharmacokinetics:

-They are pro-drugs. (Need to be activated in the body).
-All are taken orally **as enteric coated capsules (unstable in acidic medium) (coated because they need protection from the acidity of the stomach to reach the intestine)**
-Esomeprazole & pantoprazole are also available in IV formulation.(we use IV forms in patients with active peptic ulcer "bleeding").
-They are rapidly absorbed from the intestine & converted to active form.

- **Activated in the acidic medium of parietal cell canaliculi**
- **Inactivated if at neutral pH (# combined with H2 blockers or antiacids)**
- **Have long duration of action (> 12 h-24 h)**
- **Once daily dose is sufficient**
- **Given 1 h before meal.**
- **Bioavailability is reduced by food**
- **metabolized in the liver by Cyt-P450**
- **Dose reduction is required in severe liver failure**

-How Gastrooesophageal Reflux could be managed?

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

Side Effects:

-Headache, Diarrhea, abdominal pain, 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).

-prolonged acid suppression leads to:

-Subnormal B12 levels.(**Vitamin B12 deficiency**)

-Risk of hip fracture if taking PPIs over a long period. (PPIs may reduce calcium absorption or inhibit osteoclast function).

-Achlorhydria >> mucosal hyperplasia >> Colonization & infection of the stomach & intestine from ingested bacteria; increased risk of both community-acquired respiratory infections & nosocomial pneumonia. (because the bacteria in the stomach are killed by the acidity so if we decrease the acidity the risk for infection increases!)

Note: Despite all the above PPIs are very save drugs, but not preferred to be used in long periods. (if the patient needs to use PPIs for long time, he should switch it with H2 blockers to avoid the side effects).

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 (7-10 days):

- PPIs bid
- Clarithromycin, 500 mg bid (Protein synthesis inhibitor)
- Amoxicillin, 1 g bid (Cell wall synthesis inhibitor). (**Or metronidazole, 500 mg bid.)**

Note bid: twice daily, tid: three times daily.

We give high dose of Amoxicillin (1gram) and we give it twice, because we don't care about plasma level we concern about the site of H.pylori which is the stomach.

Maintenance therapy for PUD

maintenance therapy includes the following:

- Cimetidine 400 mg at bedtime is the least expensive and should be used as the medication of first choice.
- PPIs should be used as a maintenance medication only if H_2 blockers fail or cannot be used.
- The patient should be evaluated after six months

Maintenance anti-ulcer therapy will only be approved after consultation and approval by a gastroenterologist

Summary

- Test for *H. pylori* prior to beginning therapy.
- Acid-reducing medications for PUD include the following:
  - H_2RAs
  - PPI's should be used for acute therapy only if H2RAs fail or cannot be used, or as part of treatment for *H. pylori*.
- *Complete H. pylori eradication is required* to prevent relapse.
- Maintenance therapy can be given until *successful H. pylori eradication.*

	Proton Pump Inhibitors (PPIs)	**H2 receptor blockers**
e.g	Omeprazole – Lansoprazole Pantoprazole - Raprazole	Cimetidine - Ranitidine Famotidine - Nizatidine
Mechanism of action	irreversible inhibition of proton pump (H+/ K+ ATPase) that is responsible for final step in gastric acid secretion from the parietal cell.	They competitively and reversibly block H_2 receptors on the parietal cells.
Pharmacodynamics	Produce marked inhibition of basal and stimulated-acid secretion. They are the most potent inhibitors of acid secretion available today.	-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
Pharmacokinetics	-Given orally as enteric coated capsules (unstable in acidic medium). -Pantoprazole is also available in IV formulation**.** -prodrugs -rapidly absorbed from the intestine. -Activated in the acidic medium of parietal cell canaliculi. -Inactivated if at neutral pH (# combined with H2 blockers or antiacids). -Have long duration of action (> 12 h-24 h). -Once daily dose is sufficient -Given 1 h before meal. -Bioavailability is reduced by food. -metabolized in the liver by Cyt-P450. -Dose reduction is required in severe liver failure.	-Good oral absorption -Given before meals -Famotidine is the most potent drug. -Exposed to first pass metabolism (except nizatidine that has 100 % bioavailability). -Duration of action (4-12 h). -Metabolized by liver. -Excreted mainly in urine. -Cross placenta & excreted in milk (should not be given in pregnancy unless it is necessary).

uses	1-Eradication of H. pylori (combined with antimicrobial drugs). 2-Hypersecretory conditions as Zollinger Ellison syndrome and gastrinoma(First choice). 3-Resistant severe peptic ulcer (4-8 weeks). used for acute therapy only if H2RAs fail or cannot be used 4-Reflux esophagitis	1-Gastroesophageal reflux disease (GERD). 2-Acute ulcer healing -Duodenal Ulcer (6-8 weeks). -Benign gastric ulcer (8-12 weeks). 3-Post–ulcer healing maintenance therapy. 4-Pre-anesthetic medication (to prevent 5- aspiration pneumonitis). 6-Zollinger Ellison Syndrome (large doses).
Adverse effects	-Headache, diarrhea & abdominal pain. - Achlorhydria - Hypergastrinaemia. - Gastric mucosal hyperplasia. - Increased bacterial flora - increased risk of community-acquired pneumonia - Long term use: - Vitamin B12 deficiency - increased risk of fractures	-GIT disturbances (Nausea & Vomiting). -CNS effects: Headache - confusion (elderly – hepatic /renal dysfunction). -Bradycardia and hypotension (rapid I.V.) -CYT-P450 inhibition (Only Cimetidine) decrease metabolism of warfarin, phenytoin, benzodiazepines. Endocrine effects (Only Cimetidine) ▪ Galactorrhea (Hyperprolactinemia) ▪ Antiandrogenic actions (gynecomasteia – impotence) due to inhibition of dihydrotestosterone binding to androgen receptors.

which one of these drug is a prodrug ?
a. Famotidine b.Nizatidine c.Omeprazole

which one of these drug is first choice for Zollinger Ellison Syndrome ?
a.Cimetidine b.Raprazole c.Ranitidine

which one of these drug we can't use it with warfarin?
a.Nizatidine b.Cimetidine c.Ranitidine

We have quoted a lot from 430 team work, so we thank them a lot!