MED438

pharmacology
Team 438

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H2 Receptors And Proton Pump Inhibitors

Objectives:

By the end of the lecture , you should know:

- Understand the key points of pathophysiology of the peptic ulcer disease
- Enumerate various classes of drugs used in peptic ulcer disease
- Know the characteristic pharmacokinetics, pharmacodynamics and side effects of drugs used in peptic ulcer disease.
- Know the cytoprotective drugs mainly misoprostol and its use in NSAIDs-induced peptic ulcer.
- Identify different antacids that are used to relief pain of peptic ulcer.
- Identify potential adverse drug interactions of anti-ulcer drugs.

Color index:

Black : Main content
Red : Important
Blue: Males' slides only
Purple : Females' slides only
Grey: Extra info or explanation
Green : Dr. notes

Editing File

Peptic Ulcer Disease (PUD)

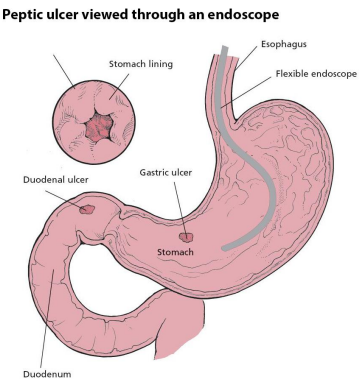
A localized lesion of the mucous membrane of the stomach **(gastric ulcer)** or duodenum **(duodenal ulcer)**, typically extending through the muscularis mucosa.

Pathophysiology

It is an <u>imbalance</u> between:

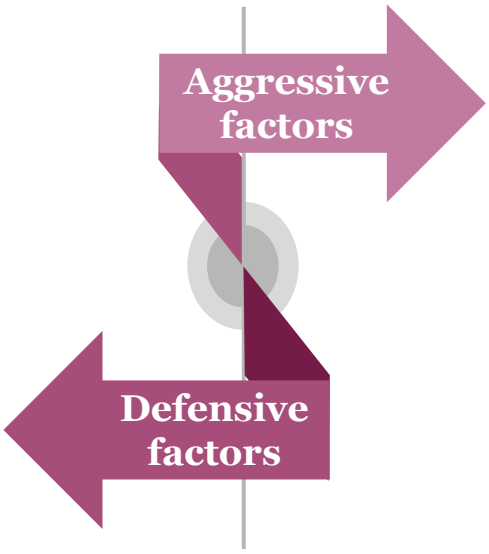
1. aggressive factors **(acid & pepsin)**
2. defensive factors **(e.g. prostaglandins, mucus & bicarbonate layer)**.

However, nowadays, it seems that **H. pylori theory**[1] is very important.



1. **Mucus**[2] **and bicarbonate**[3] **ion** secretions protect mucosa
2. **Prostaglandins** (PGE2 & PGI2) protect mucosa by:

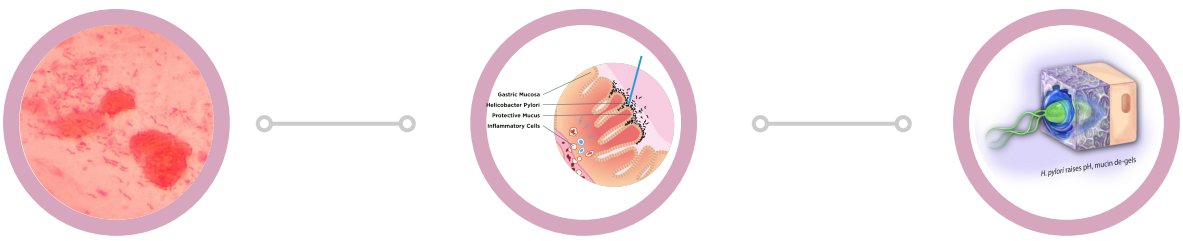
- Inhibiting acid secretion.
- Increasing mucus and bicarbonate production
- Enhancing mucosal blood flow.



1. Hydrochloric acid (HCl)
2. pepsin

What do they do?
destroy gastric and duodenal mucosa

Helicobacter Pylori



gram-negative bacterium

- **Helicobacter Pylori** is the major etiological factor in peptic ulcer disease (95% in duodenal and 80% in gastric ulcer).

1: suggests that the presence of an H.pyroli infection is the leading cause of the increase of HCl production in the stomach, which is important in changing the diagnostic & treatment approaches for peptic ulcer.
2: protects the stomach from its acidity
3: Acts as a buffer to create a neutral medium in the mucosa (neutralizes the acidity of HCl)

Etiology

- H. Pylori infection[1]
- Genetic factors
- Diet[3]
- Hypersecretory states (Zollinger Ellison syndrome)
- Caffeine[2]
- Drugs (e.g.) NSAIDs; corticosteroids
- Alcohol
- Smoking

Zollinger Ellison syndrome

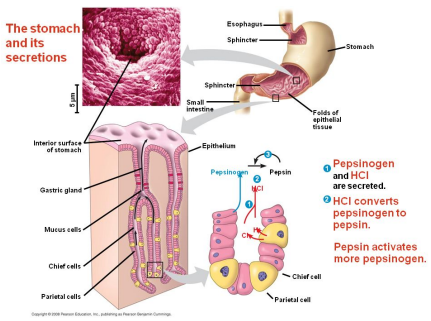
Is a disease in which **tumors** cause the stomach to produce too much acid, resulting in peptic ulcers.
symptoms include abdominal pain and diarrhea.

Gastrin produces

- **Parietal cell hyperplasia (Trophic factor)**
- **diarrhea**
- **Excessive gastric acid production**

Gastric secretions

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



Regulation of gastric secretions

Parietal cells secrete acid in response to:

1. Ach (neurotransmitter): M3 receptors
2. Gastrin(hormone): **CCK2 receptors** (cholecystokinin)
3. Histamine (local hormone): H2 receptors
4. Proton pump (H+/ K+ ATPase)

1: H.pylori infections should be excluded before the start of the treatment, because the use of hyposecretory drugs in treating H.pylori instead of antibiotics will lead to recurrent peptic ulcer.
2: increases the gastric acid secretion
3: E.g.: spicy food

Treatment Of Peptic Ulcer

1. Hyposecretory drugs[1]:
- Proton pump inhibitors[2]
- H2 receptor blockers[2]
- Antimuscarinic drugs

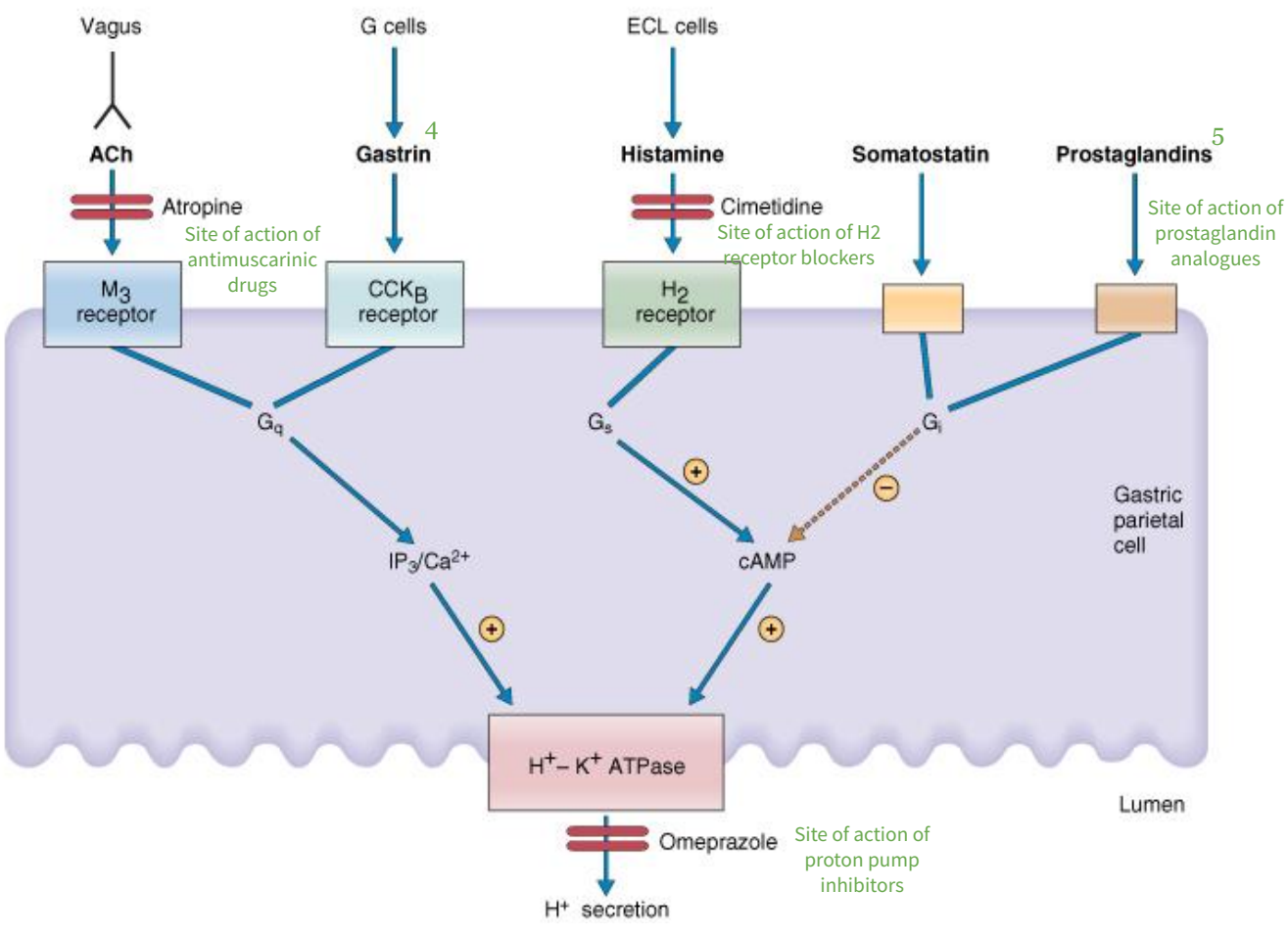
2. Mucosal cytoprotective agents[3]
- Prostaglandin analogues

3. Neutralizing agents
- antacids

4.Eradication of H. pylori infections
- Combination of Metronidazole/ Clarithromycin and PPIs)

Gastric hyposecretory drugs

Hyposecretory drugs **decrease gastric acid secretion** →Promote healing & relieve pain. Include:
- Proton pump inhibitors
- H2 receptor blockers
- Antimuscarinic drugs



1: First line treatment of peptic ulcer after excluding H.pylori infection.
2: both are widely used, but H2 receptor blockers are usually used first because they are cheaper.
3: increase turnover rate instead of decreasing the production of HCl.
4: No discovered drugs can be used safely to block CCK_B receptor.
5:prostaglandins themselves cannot be used due to very short duration of action, so we use prostaglandin analogues.

Proton Pump Inhibitors (PPIs)

Drug	Omeprazole	Lansoprazole	Pantoprazole	Raprazole
M.O.A	• Acts by **irreversible inhibition of proton pump (H+/ K+ ATPase)** that is **responsible for final step in gastric acid secretion** from the parietal cell (they covalently bind to the pump).			
P.D	• They are **the most potent inhibitors** of acid secretion available today. • Produce marked inhibition of basal & meal stimulated-acid secretion(90-98%). • Reduce pepsin activity. • Promote mucosal healing & decrease pain. ★ Proton pump inhibitors **heal ulcers faster than H2 blockers** and have **H. pylori inhibitory properties**[1].			
P.K	• Given orally , are pro-drugs. • Given as enteric coated formulations (unstable in acidic medium in stomach). • Are rapidly absorbed from the intestine. ★ Are **activated within the acidic medium** of parietal cell canaliculi[2]. ★ At neutral pH, PPIs are inactivated. ★ Should not be combined with H2 blockers or antacids[3]. • Bioavailability is reduced by food. • Given one hour before the meal. • Have long duration of action (> 12 h-24 h). • Once daily dose is sufficient. • Metabolized in the liver by Cyt-P450 • dose reduction is required in severe liver failure.			
Uses	★ Eradication of H. pylori (combined with antimicrobial drugs). • Resistant severe peptic ulcer (4-8 weeks). • Gastroesophageal reflux disease (GERD). • Hypersecretory conditions as **Zollinger Ellison syndrome and gastrinoma** (First choice).			
ADRs	• **CNS:** headache • **GIT:** diarrhea , abdominal pain **Short term use is safe but long may lead to:** • **Achlorhydria & Hypergastrinemia**[5] • Gastric mucosal hyperplasia • **Infections:** ○ Increased bacterial flora ○ Increased risk of community-acquired respiratory infections & nosocomial Pneumonia. ○ increased risk of enteric infections including C.Difficile and bacterial gastroenteritis. **Long term use can lead to:** • Vitamin B12 deficiency[6] • Hypomagnesemia • Decrease calcium absorption → Osteoporosis → increased risk of hip fractures • Decrease iron absorption			
Pre-caution	• Do not combine Omeprazole (**CYP2C19 inhibitor**) and clopidogrel (an antiplatelet), because (CYP2C19) is required for activation of clopidogrel .			

1: It has bactericidal effect, but treatment of H.pylori infections requires triple or quadruple therapy (so it cannot be used alone for H.pylori infections).
2: AFTER being absorbed by the intestines, it enters the blood circulation and from there to the parietal cells.
3: They decrease the acidity in parietal cells which prevents the activation of PPIs
5: Parietal cells send negative feedback signals to the brain when a decrease in HCl levels is sensed, which will lead to increase production of gastrin, but this increase in gastrin will not be effective in increasing the HCl as the ultimate pathway (proton pump) for HCl production is inhibited and this will lead to increase the livel of gastrin in the blood.
6: Vitamin B12, magnesium and calcium require acidic medium for their absorption.

H2 receptor blockers

Drug	Cimetidine Most Toxic	Ranitidine	Famotidine	Nizatidine
M.O.A	• They **reversibly and competitively** block H2 receptors on the parietal cells.			
P.K	• Good oral absorption • Given before meals ★ **Famotidine** is the most potent drug..	• Duration of action (4-12 h). • Metabolized by liver. • Exposed to first pass metabolism **except nizatidine** that has the greatest bioavailability • Excreted mainly in urine.		
Action	• Reduce basal and food stimulated-acid secretion . • **Block 90% of nocturnal acid secretion**[1] (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).
	  ○ Prevention of bleeding from stress-related gastritis.
	• Preanesthetic medication (to prevent aspiration pneumonitis).
	• Post–ulcer healing maintenance therapy.			

ADRs	**Serious adverse effects are RARE**
	• **GIT**: Nausea & vomiting.
	★ **CNS**: Headache - confusion[2] (in elderly, hepatic dysfunction[3], renal dysfunction[3]).
	★ Bradycardia and hypotension (if given rapid I.V.)
	★ **Only Cimetidine[4]:**
	• CYT-P450 inhibition **decrease** metabolism of warfarin, phenytoin, benzodiazepines.
	• Endocrine effects
	  ○ **Galactorrhea** (Hyperprolactinemia)
	  ○ **Antiandrogenic actions** (gynecomastia –impotence) due to inhibition of dihydrotestosterone binding to androgen Receptors.			

Pre-caution	• Dose reduction in severe renal or hepatic failure and elderly.			

	Cimetidine	Ranitidine	Famotidine	Nizatidine
Efficacy[5]	+++	+++	+++	+++
Potency[6]	+	++	+++	++
Dose	**400 mg bid**	**150 mg bid**	**20 mg bid**	**150 mg bid**
CYT P450	++	-	-	-
Antiandrogenic	++	-	-	-
Drug interactions	**Many**	**No**	**No**	**No**

1: It was found that H2 receptor pathway is the main HCl secretory pathway at **night**.
2: drug hangover effect, mainly in elderly.
3: because they are metabolized in the liver and excreted in the kidney.
4: Cimetidine not used clinically in the treatment of peptic ulcers due to those side effects
5: all of them have equal efficacy.
6: less potency = higher dose of the drug is used to achieve the same effect of a drug of a higher potency.

Prostaglandin analogues

Drug	Misoprostol
M.O.A	• Prostaglandin analogues (PGE1) • ↓HCL secretion • ↑protective measures[1] (↑ mucous \ bicarbonate & gastric mucosal blood flow)
P.K	• Orally , must be taken 3-4 times / day
Uses	★ Drug of choice for NSAIDs - induced peptic ulcer, e.g arthritis ● labor induction
ADRs	• Abdominal cramps; diarrhea. • Uterine contraction (dysmenorrhea or abortion). • Vaginal bleeding

Antacids

Drug	Inorganic salts[2]: NaHCO3 | CaCO3 | Al(OH)3 | Mg(OH)2
M.O.A	• Acts by **direct chemical neutralization** of HCL and decrease pepsin activity.
Uses	• Used to **relieve pain**[3] of peptic ulcer & for dyspepsia. • All antacids ↓ absorption of some drugs as tetracycline, fluoroquinolones, iron. Not used frequently for gastric and duodenal ulcers because they cause rebound acidity.
ADRs	• **NaHCO3 (Sodium bicarbonate):** ○ Effective, but systemic alkalosis[4] may occur ○ **Contraindicated** In CVS patients[5] • **Aluminum hydroxide[6] :** Mnemonic: CHOPS ○ Constipation ○ Hypophosphatemia[7] (Proximal weakness , malaise , anorexia) ○ Osteodystrophy ○ Seizures. • **Magnesium hydroxide:** ○ Diarrhea ○ Cardiac arrest, hypotension • **Calcium carbonate :** ○ Milk-alkali syndrome[8] ○ Hypercalcemia ○ Renal failure ○ ↓ absorption of tetracycline.

1:AKA: cytoprotection, Not considered as a mechanism of action when treating peptic ulcer due to re-flaring of the ulcer by acidic food.
2: Basic compounds. 3: Only relief the pain, they are NOT an actual treatment
4: Bicarbonate will produce carbonic acid which will dissociate into H_2O and CO_2 leading to alkalosis
5: it contains Na, so hypernatremia can happen.
6: usually found in one packet with magnesium hydroxide to oppose their (constipation + diarrhea) actions
7: aluminium antagonizes phosphate.
8: Carbonate produces an alkaline medium that leads to the calcification of calcium = kidney stones and kidney failure

Quiz

MCQ

1- A 45-year-old woman complains of persistent heartburn and an unpleasant, acid-like taste in her mouth. The clinician suspects that she has gastroesophageal reflux disease and advises her to raise the head of her bed 6 to 8 inches, not to eat for several hours before retiring,and to eat smaller meals. Two weeks later, she returns and says the symptoms have subsided slightly but still are a concern. The clinician will likely prescribe which one of the following drugs?

A- an antacid such as aluminum hydroxide B- Dicyclomine
C- An antianxiety agent such as alprazolam D- Lansoprazole

2-Which of the following medications for gastrointestinal problems is contraindicated in pregnancy?

A- Calcium carbonate B- Famotidine C- Lansoprazole D- Misoprostol

3- An elderly woman with a recent history of myocardial infarction is seeking a medication to help treat her occasional heartburn. She is currently taking several medications, including aspirin, clopidogrel, simvastatin, metoprolol, and lisinopril. Which of the following choices should be avoided in this patient?

A- Famotidine B- Calcium carbonate C- Omeprazole D- Ranitidine

4- A patient came complaining from impotence and gynecomastia. After taking history , he revealed that he had a recent peptic ulcer which he took medication for. Which of the following drugs was he on?

A- Ranitidine B- Cimetidine C- Famotidine D- Omeprazole

5- Which adverse effect of H2 receptor blockers will be most evident in elderly patients , or with patients with hepatic\renal dysfunction ?

A- Nausea and vomiting B- Bradycardia C- Galactorrhea D- Headache and confusion

SAQ

1- A 48 years old patient was taking medication for back pain for a long time, later he developed an epigastric pain, nausea and vomiting.
Q1-What is the best drug to be used in this case ?
Q2- What is the M.O.A of the drug ?

Q3-A patient comes complaining of epigastric pain and heartburn that wakes him up during his sleep at night. Drug history of the patient reveals that he is on warfarin. What is the best drug to be prescribed in this case?

4- A 59 years old male came to the ER complaining of abdominal pain , diarrhea , nausea and vomiting for 2 days , the blood test shows high level of gastrin and the other investigations proof the diagnosis of Zollinger Ellison syndrome.
Q4-Which class of hyposecretory drugs can be used in this case ?
Q5-List 2 common side effect of those drugs.

Answers:

MCQ

Q1	D
Q2	D
Q3	C
Q4	B
Q5	D

SAQ

Q1	Misoprostol
Q2	Decrease HCL secretion-Increase protective measures (↑mucous bicarbonate & gastric mucosal blood flow)
Q3	Famotidine
Q4	Proton pump inhibitors
Q5	Achlorhydria & hypergastrinemia - Vitamin B12 deficiency upon long term use.

Share with us your ideas !

Good Luck , Future Doctors!

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