Lecture 2

Drugs in peptic ulcer
(H_2 blockers and proton pump inhibitors)

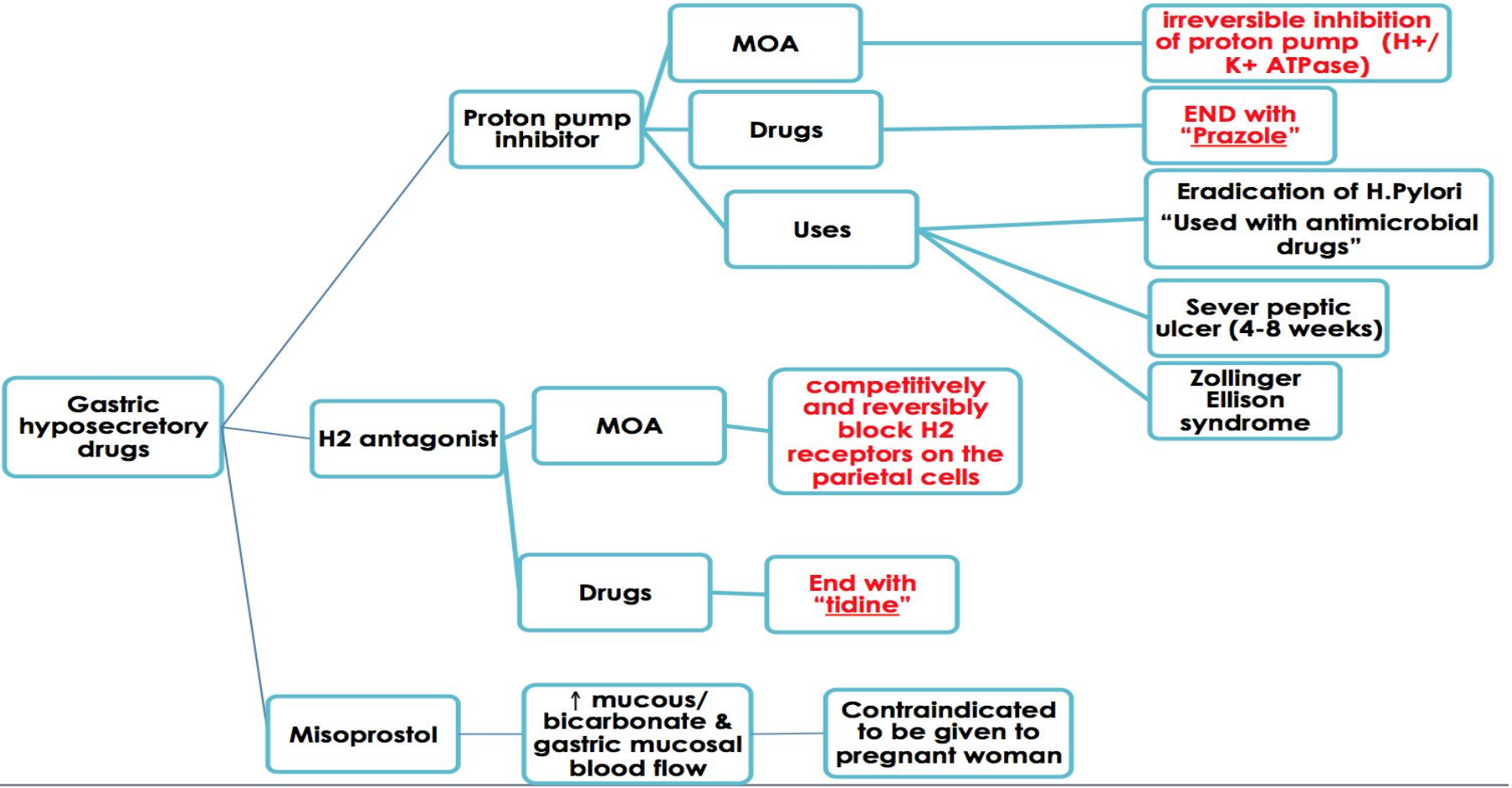
Objectives:

- ★ Classify the main different classes of hyposecretory drugs used for treating peptic ulcer.
- ★ Know the characteristic pharmacokinetics, pharmacodynamics and side effects of proton pump inhibitors, and H2 receptor blockers.
- ★ 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.

- Additional Notes
- Important
- Explanation –Extra-

For any correction, suggestion or any useful information
do not hesitate to contact us: Pharmacology434@gmail.com

mind map



before starting, please check our GIT block correction

introduction

peptic ulcer:

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

2-pathophysiology: is 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.

3-etiology (risk factor) :

- **H. pylori infection** (most common)
- Alcohol
- Smoking
- Caffeine
- Genetic factors (O blood group)
- Diet
- Drugs (e.g.) NSAIDs
- Hypersecretory states: (Zollinger Ellison syndrome)

gastric secretion:

A-site of secretion:

1.**HCl and intrinsic factor** → **Parietal cells** (so acid secretion is mainly here)

2.**Pepsinogens** → **Chief cells**

3.**Mucus, bicarbonate** → **mucus-secreting cells**

C- Treatment:

by knowing the regulation of gastric secretion we can predict the treatment therapy:

1-Eradication of H. pylori infections

(combination of metronidazole/ clarithromycin and PPIs)

use in recurrent PUD

2-Hyposecretory drugs.

decrease gastric acid secretion promote healing & relieve pain

- **Proton pump inhibitors** (best)
- **H_2 receptor blockers** (better than antimuscarinic)
- **Antimuscarinic drugs**

3-Mucosal cytoprotective agents.

- **Prostaglandin analogues**

4-Neutralizing agents (antacids).

B-regulation of gastric secretion:

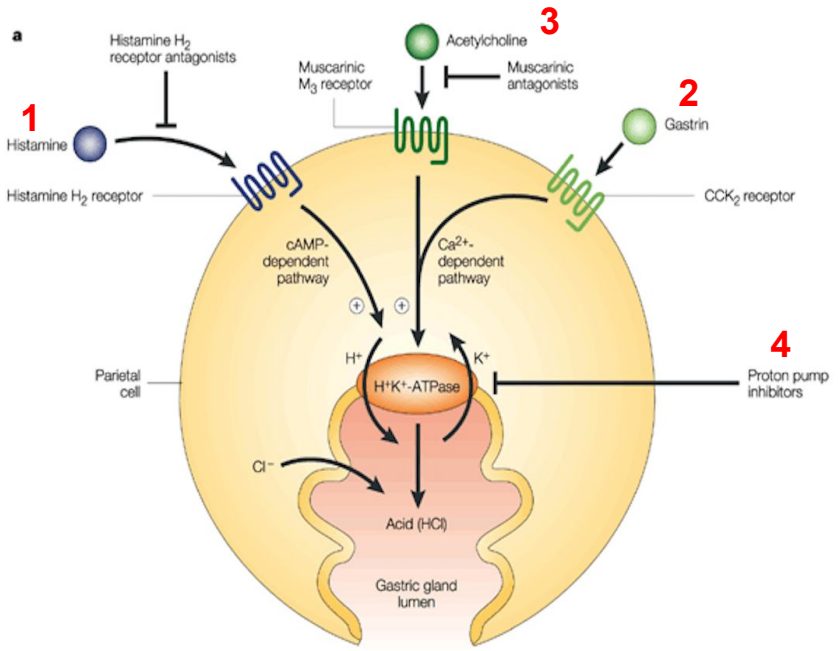
Parietal cells secrete acid in response to:

1.**Histamine (local hormone): H_2 receptors**

2.**Gastrin (hormone): CCK_2 receptors**

3.**Ach (neurotransmitter): M_3 receptors**

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



1-Proton Pump Inhibitors (PPIs)

Drugs	**Omeprazole , Lansoprazole , Pantoprazole , Raprazole**
Mechanism	Irreversible inhibition of Proton pump (H+ / K+ atpase) that responsible for final step in gastric acid secretion from parietal cells
Pharmaco-dynamic	• the most potent inhibitors of acid secretion these days • produce inhibition of basal and meal stimulated acid secretion (90-98%) • reduced pepsin activity + promote mucosal healing and decrease the pain
Pharmaco-kinetics	• Given orally as enteric coated capsules* (unstable in acidic medium in stomach). *It means not dissolved unless reaching the intestine • Are pro-drugs (it get activated after administered). *Dose reduction is required in severe liver failure • rapidly absorbed from the intestine. • in the acidic medium of parietal cell canaliculi, they are **activated**. • Should not combined with **H2 blockers** or **antacids**.*because H2 blockers+antacid decrease acidity and PPIs need an **acid medium** to get activated • At neutral pH, PPIs are inactivated. Once daily dose is sufficient . Bioavailability is reduced by food. • Have long duration of action (> 12 h-24 h) Given 1 h before meal. • metabolized in the liver by Cyt-P450.

Cont. 1-Proton Pump Inhibitors (PPIs)

Uses

- Eradication of H. pylori (combined with antimicrobial drugs).
- Resistant Severe Peptic Ulcer(4-8)weeks.
- Reflux Esophagitis.
- Hypersecretory conditions as **Zollinger Ellison syndrome** and gastrinoma* **(First choice)**

Zollinger Ellison syndrome: is Gastrin -secreting tumor of the pancreas.

Gastrin produces:

1-Parietal cell hyperplasia (trophic factor) 2-Excessive gastric acid production.

Adverse effects

- CNS : Headache, GIT : diarrhea ,abdominal pain.
- Achlorhydria(gastric acid in stoma is decreased or absent, no secretion of HCl)
- Hypergastrinemia*(the presence of excess gastrin in blood, compensatory mechanism of decrease HCL)
- decreased HCL.
- Gastric Mucosal Hyperplasia (as a result of increased gastrin secretion)
- Increased Bacterial Flora
- Increased Risk Of Community-acquired respiratory Infections nosocomial pneumonia

*Long term use:

- 1) vitamin B12 deficiency.
- 2) increased risk of hip joint fractures.

2- H2 receptor blockers

drugs	**Cimetidine,Ranitidine,Famotidine, Nizatidine**
Mechanism of action	They competitively and reversibly block **H_2 receptors** on the parietal cells.
Pharmacokinetics	• Good oral absorption. • Given before meals. • **Famotidine** is the most potent drug. • Exposed to first pass metabolism (except nizatidine that has greatest bioavailability). • Duration of action (4-12 h) Metabolized by liver. • Excreted mainly in urine.
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

Cont. 2-H2 receptor blockers

Uses	• GERD (heartburn/ dyspepsia). • Acute ulcer healing in moderate cases • Duodenal Ulcer (6-8 weeks). • Benign gastric ulcer (8-12 weeks). • Pre-anesthetic medication. • Prevention of bleeding from stress-related gastritis. • Post–ulcer healing **maintenance therapy**.
Adverse effects	• **Minor GIT disturbances** (Nausea & Vomiting). • **CNS effects**: Headache - confusion (elderly, hepatic dysfunction, renal dysfunction). • Bradycardia and hypotension (rapid I.V.) • **CYT-P450 inhibition** (Only Cimetidine) decreases metabolism of warfarin, phenytoin , benzodiazepines. • **Endocrine effects** (Only Cimetidine): 1-**Galactorrhea** (Hyperprolactinemia), 2-**Antiandrogenic actions** (gynecomasteia –impotence) due to inhibition of *dihydrotestosterone* binding to androgen receptors.
Precautions	• Dose reduction of H_2 RAs in **severe renal** or **hepatic failure** and **elderly**.

3- Antacids:

- These drugs are mainly inorganic salts.

$NaHCO_3$, $CaCO_3$, $AL(OH)_3$, $Mg(OH)_2$. (not a chemistry lecture ☺)

Mechanism of Action :

- acts by direct chemical neutralization of HCL and as a result may decrease pepsin activity.

Antacids Indications :

- used to relieve pain of peptic ulcer & for dyspepsia.

Antacids and Drugs Absorption :

- All antacids **decrease** absorption of some drugs as (*tetracycline ,fluoroquinolones ,iron*).

Antacids Side Effects :

- **$NaHCO_3$:** (systemic alkalosis).
- **$CaCO_3$:** milk alkali syndrome (hypercalcemia , renal failure).
- **$AL(OH)_3$:** constipation.
- **$Mg(OH)_2$:** Diarrhea.

4- Prostaglandin analogues (PGE1)

Misoprostol :

- Prostaglandin analogues (**PGE1**) which is *cytoprotective*.

Mechanism of Action :

- decrease HCL secretion.
- increase mucous and bicarbonate secretion , increase gastric mucosal blood flow. (protective measures)
- Must be taken 3-4 times/day. (rarely used because of short t ½)
- Orally.

Misoprostol Indications :

- Selective use in NSAID-induced peptic ulcer.

Misoprostol Side Effects :

- *Abdominal cramps* (diarrhea).
- *Uterine contraction* (dysmenorrhea , abortion) ,*vaginal bleeding*.

it is contraindicated in pregnancy

Summary

Proton pump inhibitors

Drugs	**Omeprazole - Lansoprazole - Pantoprazole - Raprazole**
Pharmacological Actions	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 are the most potent inhibitors of acid secretion available.
PharmacoKinetics	Given orally as enteric coated capsules (unstable in acidic medium in stomach) - Are pro-drugs - rapidly absorbed from the intestine - In the acidic medium of parietal cell, they are activated - Should not combined with H2 blockers or antacids.
Indication	Eradication of H. pylori (combined with antimicrobial drugs) - Resistant severe peptic ulcer (4-8 weeks) - Reflux esophagitis - Hypersecretory conditions as Zollinger Ellison syndrome and gastrinoma (First choice).
Adverse effects	Headache, diarrhea & abdominal pain- Achlorhydria - Hypergastrinaemia - Gastric mucosal hyperplasia - Increased bacterial flora - increased risk of community-acquired respiratory infections & nosocomial pneumonia *Long term use: Vitamin B12 deficiency - increased risk of hip fractures

Summary

H2 Receptor Blockers

Drugs	**Cimetidine - Ranitidine - Famotidine - Nizatidine**
Pharmacological Actions	They competitively and reversibly block H2 receptors on the parietal cells - 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	Good oral absorption - Given before meals - Famotidine is the most potent drug - Exposed to first pass metabolism (except nizatidine that has greatest bioavailability) - Duration of action (4-12 h) - Metabolized by liver - Excreted mainly in urine.
Indication	GERD ((heartburn/ dyspepsia) - Acute ulcer healing in moderate cases - Duodenal Ulcer (6-8 weeks) - Benign gastric ulcer (8-12 weeks) - Pre-anesthetic medication - Prevention of bleeding from stress-related gastritis - Post–ulcer healing maintenance therapy.
Adverse effects	Minor, GIT disturbances (Nausea & Vomiting) - CNS effects: Headache - confusion (elderly, hepatic dysfunction, renal dysfunction) - Bradycardia and hypotension (rapid I.V.) -CYT-P450 inhibition (Only Cimetidine) decrease metabolism of warfarin, phenytoin, benzodiazepines. -Only Cimetidine has Endocrine effects: Galactorrhea (Hyperprolactinemia) - Antiandrogenic actions (gynecomasteia –impotence) due to inhibition of dihydrotestosterone binding to androgen receptors. Precautions: Dose reduction of H2 RAs in severe renal or hepatic failure and elderly.

MCQs

1. Which of the following is unstable in acidic medium and should be given as an enteric coated capsule?
   A. Pantoprazole
   B. Famotidine
   C. Misoprostol
   D. NaHCO3

2. Patient with peptic ulcer disease treated with one of gastric hyposecretory drug , after a long time he developed megaloblastic anemia due to vit B12 deficiency, What is the drug that this patient uses?
   A. Misoprostol
   B. Omeprazole
   C. Famotidine
   D. Antacids

3. Patient treated with omeprazole, What are the side effect of this drug?
   A. Glactorrhea
   B. Hypergastrinemia
   C. Milk alkali syndrome
   D. vaginal bleeding

4. As a gastroenterologist, you recommend the use of a histamine H2-blocker for a patient who has a history of atrial fibrillation, for which he takes warfarin. Your office receives a call from his primary physician, who has admitted the patient for warfarin toxicity. Which of the following H2-blockers has the patient likely been taking?
   A. Nizatidine
   B. Ranitidine
   C. Cimetidine
   D. Misoprostol

5. A 34-year-old man is seen over multiple visits for complaints of ‘‘ulcers,’’ despite the use of ranitidine. Further studies, finding elevated levels of gastrin and evidence of ulcers involving the jejunum, suggest a diagnosis of Zollinger-Ellison syndrome. Which of the following agents would be most useful in the management of this patient?
   A. Famotidine
   B. Misoprostol
   C. Lansoprazole
   D. Cimetidine

MCQs

6. Which of the following should not be used in a case of a pregnant woman?

A. Nizatidine
B. Lansoprazole
C. Antacids
D. Misoprostol

7. a 24 male has a duodenal peptic ulcer treated with one of the gastric hyposecretary drugs, after certain time the patient return to his doctor complaining of enlargement of his breast, What is the probable drug given to this patient?

A. Ranitidine
B. Misoprostol
C. Lansoprazole
D. Cimetidine

8. Which of the following has a less first pass metabolism?

A. Nizatidine
B. Cimetidine
C. Famotidine
D. Ranitidine

Ans: 1.A 2.B 3.B 4.C 5.C 6.D 7.D 8.A

SAQs

1- name one drug and the classes for treatment of peptic ulcers:
Ans:

A-proton pump inhibitors: omeprazole and raprazole
B-H2 receptor blockers: cemitidine and ranitidine
C-prostaglandin analogues: Misoprostol

2- name two side effect that is in cemitidine and not in other drugs in the same class:
Ans:

1-Galactorrhea (Hyperprolactinemia)
2-Antiandrogenic actions (gynecomasteia –impotence)

3- name one side effect of these inorganic antacids:
Ans:

1-NaHCO3 : (systemic alkalosis).
2-CaCO3 : milk alkali syndrome (hypercalcemia , renal failure).
3-AL(OH)3 : constipation**.**
4-Mg(OH)2 : Diarrhea

Good luck!

Done by Pharmacology team

- ★ Ahmed Alsaleh
- ★ Moath aleisa
- ★ Hussain alkaff
- ★ Omar rahbeeni
- ★ Mashhoor alzareie
- ★ Moath walbi

For any correction, suggestion or any useful information do not hesitate to contact us: Pharmacology434@gmail.com