PHARMACOLOGY TEAM

Drugs used for peptic ulcer

Color Guide

Slides = Black
Females notes = Green
female slides= purple
Males slides= Blue
Explanation=Orange

This lecture was done by:
Heba alsharif & Alanoud alhoqail

And was reviewed by:
Ali Saeed Alrawdhan

peptic ulcer

Objectives:

- **Understand the key points of pathophysiology of the peptic ulcer disease**
- **Enumerate various classes of dugs used in peptic ulcer disease**
- **Correlate actions of anti-ulcer drugs with pathphysiology of the disease.**
- **Understand the mechanisms of action, routes of administration and adverse of drugs used in peptic ulcer disease.**
- **Understand the rationale of combination triple & quadruple therapy for H. pylori infected ulcers**
- **Identify potential adverse drug interactions of anti-ulcer drugs.**

peptic ulcer disease

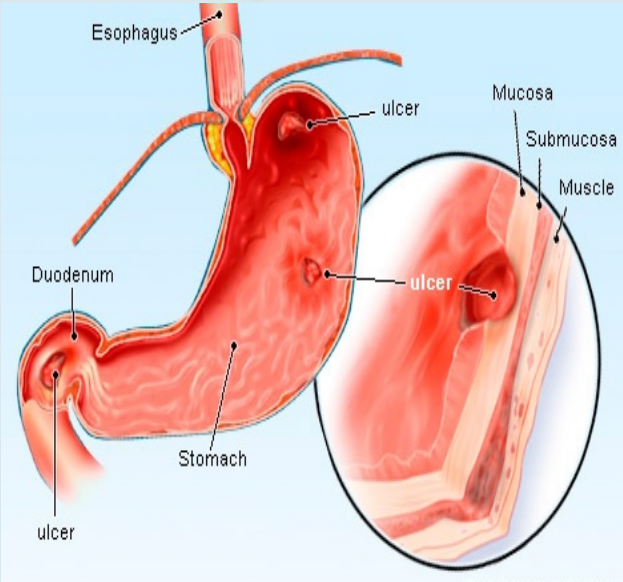
Peptic ulcer disease (PUD)

A localized lesion of the mucous membrane of the :

- stomach (gastric ulcer)
- duodenum (duodenal ulcer)

typically extending through the muscularis mucosa.

Ulceration in esophagus due to regurgitation of the gastric content



Pathophysiology

•Is imbalance between:

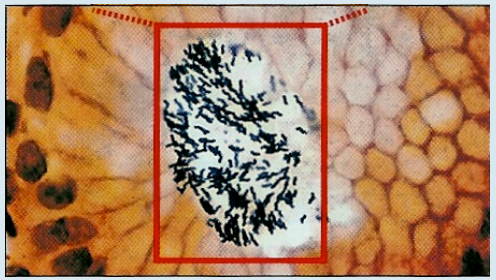
aggressive factors (acid &pepsin) + defensive factors Prostaglandins & mucus & bicarbonate layer = Peptic ulcer

•Prostaglandin is very protective for the mucosal layer special subtype E,I .

•However, nowadays, it seems that H. pylori theory is very important .

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

Prostaglandins are protective in stomach
It increases bicarbonate in mucous + blood flow and decreases HCL secretion



Pathophysiology

Hydrochloric acid and pepsin destroy gastric and duodenal mucosa.

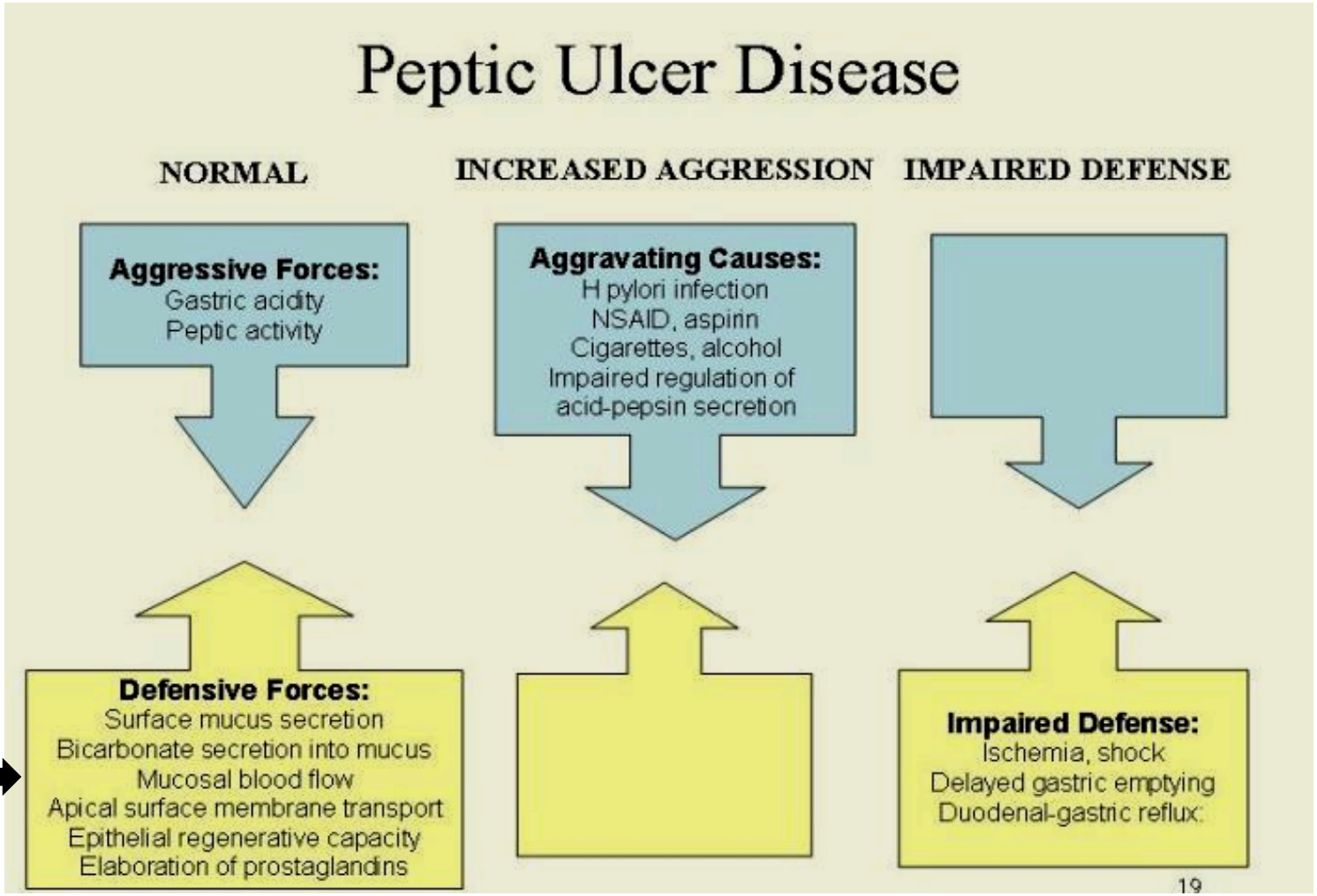
Decrease mucus and bicarbonate ion secretions that protect mucosa

Derease Prostaglandins release (PGE_2 & PGI_2) that protect mucosa by inhibiting acid secretion, increasing mucus and bicarbonate production and by enhancing mucosal blood flow. (NSAIDs)

Pathophysiology

Simply it is imbalance between Aggressive factors (Acid & Pepsin) and Defensive Factors (e.g.Prostaglandins)

Mucosal cytoprotactive agents



Pathophysiology

Etiology:

H.pylori infection number 1
- **Alcohol**
- **Smoking**
- **Caffeine (increases gastric acid)**
- **Genetic factors ex:Blood type B**
- **Diet**
- **Hypersecretory states (Zollinger Ellison syndrome)**
- **Drugs (e.g.) NSAIDs**

(NSAIDs affect the kidney and the GIT)
it increase gatrin >> increase HCL
Also it decreases prostaglandins

Zollinger Ellison syndrome

- Is characterized by excessive production of gastrin by gastrinoma of the pancreas or duodenum that stimulates parietal cells of the stomach to release excessive amounts of gastric acid.
- Gastrin produces:
  - Parietal cell hyperplasia (trophic factor).
  - Excessive gastric acid production.

A non–beta islet cell, gastrin-secreting tumor of the pancreas that stimulates the acid-secreting cells of the stomach to maximal activity, with consequent gastrointestinal mucosal ulceration.

Gastrinoma of the panceras → Hyperplasia of the parietal cells → Increase HCL

→ **hypergastremia**

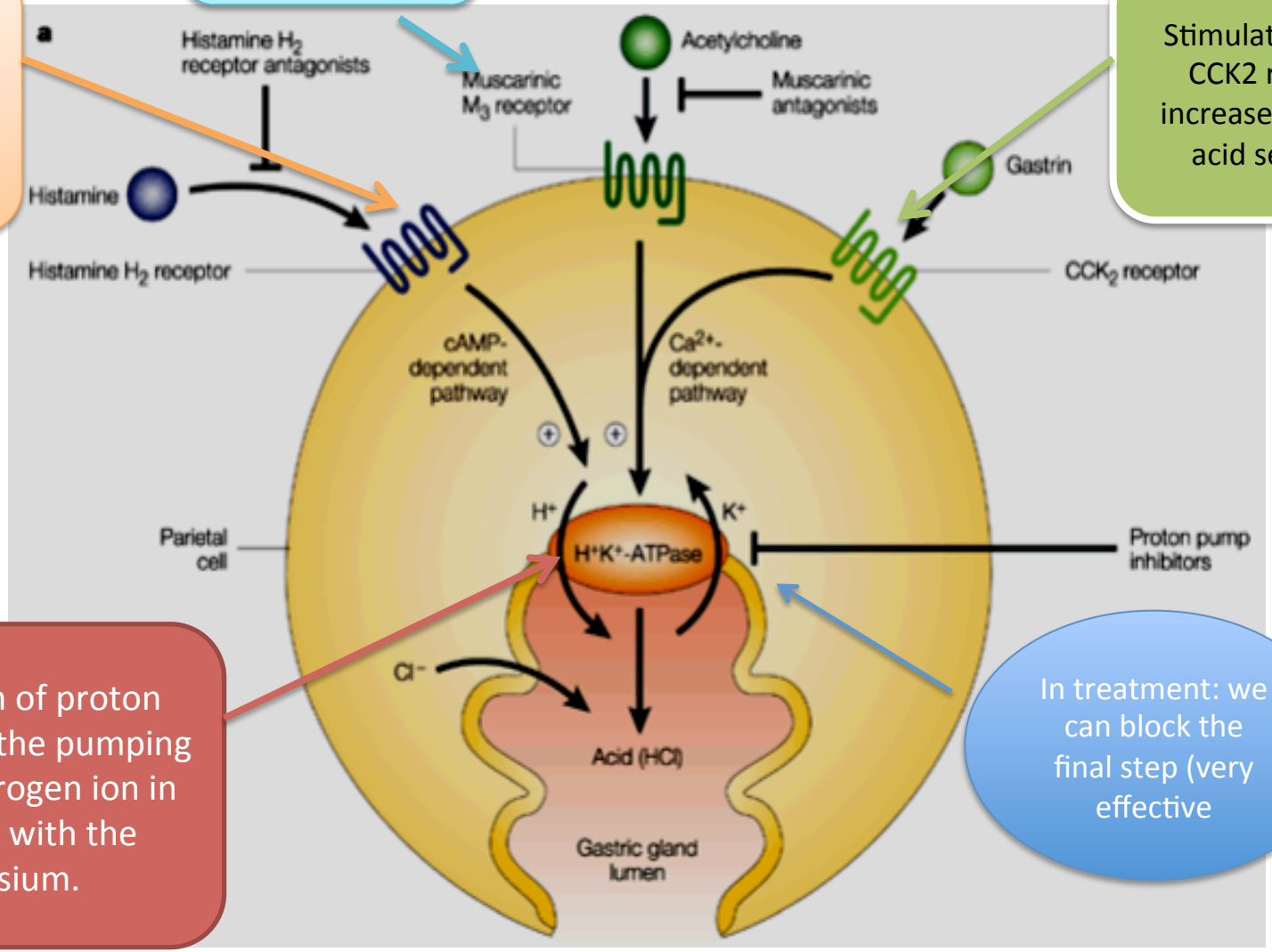
Gastric secretions	Regulation of gastric secretions
1.HCl and intrinsic factor (Parietal cells). 2.Pepsinogens (Chief cells). 3.Mucus, bicarbonate (mucus-secreting cells). (The mucus producing cells in the stomach help to form a protective lining to keep the digestive juices from digesting the stomach itself)	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) N.B. CCK_2= cholecystokinin receptors

Regulation of gastric secretions

Vagal supply of muscarinic receptor,Ach is the transmitter

Stimulation of H2 receptor increase the gastric secretion

Stimulation of the CCK2 receptor increase the gastic acid secretion



Stimulation of proton pump cause the pumping out the hydrogen ion in exchange with the potassium.

In treatment: we can block the final step (very effective

Treatment of peptic ulcer

Eradication of H. pylori infections(first step very important)

Otherwise the recurrence of ulcer increases due to increase the secretions

Hyposecretory drugs:

Proton pump inhibitors (most potent)

H_2 receptor blockers

Antimuscarinic drugs

They will **decrease gastric acid** secretion
➔Promote healing & relieve pain.

Protective measures:

Mucosal cytoprotective agents:

Prostaglandin analogues

Prostaglandins alone has short duration of action,so we give Prostaglandin analogues

Protective measures:

Neutralizing agents (antacids).

Proton Pump Inhibitors (PPIs)

Mechanism of action

Acts by irreversible inhibition of proton pump (H+/ K+ ATPase) that is responsible for final step in gastric acid secretion from the parietal cell.

The drugs are:

- **Omeprazole**
- **Lansoprazole**
- **Pantoprazole**
- **Raprazole**
- **Esomeprazole**

- **Remember PPI >> Prazole (suffix)**

Pharmacodynamics

- **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. (pepsin will be activated in the presence of HCL, so reduced gastric acid decrease the pepsin)**
- **Promote mucosal healing & decrease pain.**
- **Proton pump inhibitors heal faster the ulcers than H_2 blockers, and have H. pylori inhibitory properties. PPI one of the contents in H.pylori eradication therapy**

Proton Pump Inhibitors (PPIs)

Pharmacokinetics

- All Given orally
- Are pro-drugs (activated in the body)
- rapidly absorbed from the intestine.

(from the intestine to the bloodstream back to the stomach)

- Activated in the acidic medium of parietal cell canaliculi.(active form gives the action)
- Inactivated if at neutral pH.
- Should not combined with H_2 blockers or antacids.

(cause those two groups will decrease the acidity in the parietal cells, so by that deacresing it's activity, H2 blockers reduces the acidic meduiem requeires for activation of PPIs)

- 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.

USES

- Eradication of H. pylori (combined with antimicrobial drugs).
- Peptic ulcer (4-8 weeks) resistant to H_2 antagonists.

(Firstly we use the H2 blockers(especially moderate cases) ,if the patient is not responding we start the PPIs(expensive given in severe cases)

- Hypersecretory conditions as Zollinger Ellison syndrome (drug of choice).
- Reflux esophagitis.

Proton Pump Inhibitors (PPIs)

Adverse effects

- **Headache, diarrhea & abdominal pain.**
- **Achlorhydria**
(the production of the acid is reduced or abscent, Low HCL)
- **Hypergastrinaemia.**
- **Gastric mucosal hyperplasia.**
  - **Increased bacterial flora.**
  - **increased risk of community-acquired respiratory infections & pneumonia.**

Long term use:

- **Vitamin B_{12} deficiency**
(due to the decrease in the level of gastric intrinsic factor)
- **increased risk of hip fractures.**

PPI therapy leads to diminished acid secretion

↓

Diminished D-cell release of somatostatin(body thinks that the acis is low)

↓

consequent increased G-cell release of gastrin and hypergastrinemia.

↓

This causes oxyntic cell hyperplasia(but the praietal cells are blocked, can't produce HCL)

H_2 receptor blockers

Mechanism of action	Pharmacokinetics	pharmacological actions
• They competitively and reversibly block H_2 receptors on the parietal cells. Used more than once per day - Cimetidine - Ranitidine - Famotidine - Nizatidine	• Good oral absorption • Given before meals. • Famotidine is the most potent drug.so small doses are given • Exposed to first pass metabolism (except nizatidine that has 100 % bioavailability). • Duration of action (4-12 h). • *Metabolized by liver. • *Excreted mainly in urine. • ** be careful in case of liver or renal disorders) • Cross placenta & excreted in milk (should not be given in pregnancy unless it is necessary).	• 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.>> healing >> less pain • Promote mucosal healing & decrease pain • Reduce acid secretion stimulated by histamine, as well as by gastrin & cholinergic drugs.

H_2 receptor blockers

USES

- GERD (heartburn/ dyspepsia).
- Acute ulcer healing in moderate &mild cases.
- Duodenal Ulcer (6-8 weeks).
- Benign gastric ulcer (8-12 weeks).
- In severe cases we use PPIs (proton pump inhibitors)
- Zollinger Ellison Syndrome
- Pre-anesthetic medication (to prevent aspiration pneumonitis).
- Prevention of bleeding from stress-related gastritis.
- Post–ulcer healing maintenance therapy. (if the patient doesn't have H.pylori infection)
- Decrease the heartburn by NSAIDs
- PUD: effective in nocturnal acid suppression & ulcer healing in moderate cases

Use Famotidine better than Cimetidine cuz it requires high dose

Adverse effects

- GIT disturbances (Nausea & Vomiting).
- CNS effects: Headache – confusion (elderly they have confusion commonly, hepatic dysfunction, 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.*
  - Dose vary according to patient condition

Precautions

Dose reduction of H_2 RAs in severe renal or hepatic failure and elderly.

	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

Less potent 2times/day

The doctor focused on cimetidine

Not important to memorize dose

Antacids

Alkaline substance neutralizez acids

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

- acts by direct chemical neutralization of HCL and as a result may decrease pepsin activity.
- used to relief pain of peptic ulcer & for dyspepsia.(without healing),it may rebounds pain by increasing HCL
- All antacids ↓ absorption of some drugs as

tetracycline, fluoroquinolones, iron.

NaHCO3: Systemic alkalosis; **Ca CO3 :** milk(Ca) alkali syndrome(basic meduim) (hypercalcemialead to renal stones>, renal failurehypercalcemia)

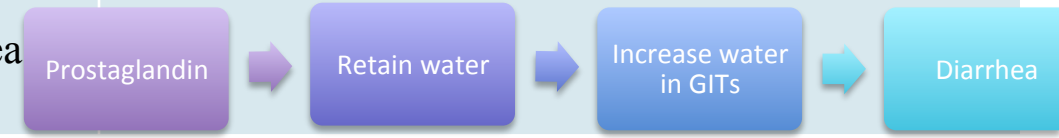
Al (OH)3 : constipation; **Mg (OH)2:** Diarrhea
**Give both to balnce

Misoprostol

- **Prostaglandin analogues (PGE1)**
- **↓ HCL secretion.**
- **↑ protective measures (↑ mucous/ bicarbonate & gastric mucosal blood flow).**
- **Orally, must be taken 3-4 times/ day,**has short duration of action**.**
- **Used for NSAIDS-induced peptic ulcer by lowring prostaglandins**

Adverse effects:

- **Abdominal cramps; diarrhea**
- **Uterine contraction (dysmenorrhea or abortion);**
- **Vaginal bleeding.** → **dont give in pregnancy**



Eradication of Helicobacter pylori

- **All PUD patients** must be evaluated for H. pylori.
- Patients with H. pylori should be treated.
- **Eradication** is important to prevent **recurrence** of ulcer.

- A combination of antibiotics and acid-reducing medicines is the most effective treatment.
  - PPIs or H_2 receptor blockers
  - Antibiotics
    - Clarithromycin
    - Tetracycline or amoxicillin
    - Metronidazole if patient allergic to penicillin.
  - Bismuth subsalicylate.
  - NO TREATMENT OF PUD WITHOUT TREATING H.PYLORI

Eradication of Helicobacter pylori

Triple therapy (First-line therapy):

1. **Proton pump inhibitors (PPIs)**
2. **Clarithromycin effective**
3. **Amoxicillin (metronidazole** is substituted for amoxicillin in patients allergic to penicillin).

Quadruple therapy (bismuth-based regimen)

1.Proton pump inhibitors (PPIs)

2.Bismuth subsalicylate (bismuth whatever the salt is)

3.Metronidazole

4.Tetracycline ,Clarithromycin is more effective

Could be changed

First we use Triple therapy for 2_3 weeks then >> test blood for H.pylori ,if it's (-) >> treat ulcer by hyposecretory drugs
If it's (+) >> Quadraple therapy

Summary

- Test for *H. pylori* before starting the therapy.
- Complete *H. pylori* eradication is required to prevent relapse.
- Acid-reducing medications are prescribed in case of PUD **without** H. pylori infections.
- Acid-reducing medications for PUD include:
  - H_2RAs (H_2 receptors antagonists).
  - PPI's should be used for acute therapy only if H_2RAs fail or cannot be used, or as part of treatment for H. pylori.
- **PUD with H pylori infections can be treated with**
- **Triple therapy** PPI's + clarithromycin + amoxicillin
- **Quadruple therapy**

PPI's + Bismuth + Metronidazole + tetracycline

Summary from 431teamwork (thanks to Wael al saleh)

Drugs used in Peptic Ulcer

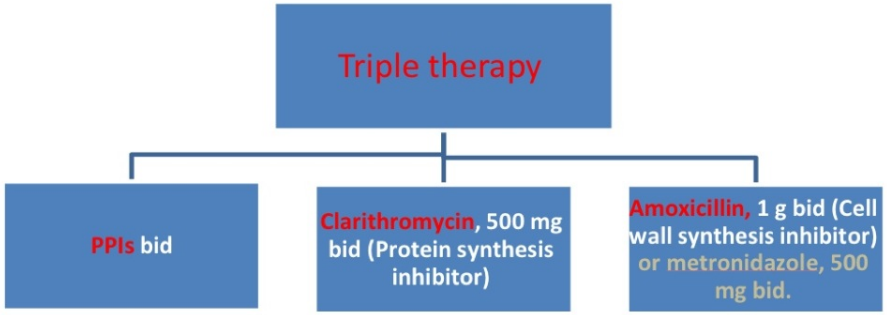
Drug	MOA	Pharmacokinetics	ADRs
1-Antiacids: These drugs are mainly inorganic salts (e.g.: $NaHCO_3$; $Ca\ CO_3$; most commonly used $Al(OH)_3$; $Mg(OH)_2$)	Antagonize acid; Also, Indirectly may decrease pepsin activity		constipation (from Al), diarrhea (from Mg), hypophosphatemia...others note: preparations that combine both Al and Mg hydroxides are used as their actions will cancel each other.
2- H2 –receptor antagonists: e.g: Cimetidine (prototype) most clinically use : Ranitidine (Zantac); Famotidine (most potent) ; Nizatidine **Used In :** • GERD (gastroesophageal reflux disease), (heartburn/ dyspepsia). • PUD(peptic ulcer disease): effective in nocturnal acid suppression & ulcer healing in moderate cases • Prevention of bleeding from stress-related gastritis. • Decrease the heartburn by NSAIDs. • Zollinger Ellison Syndrome (large doses).	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 **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. Block 90% of nocturnal acid secretion (which depend largely on histamine) ;Therefore, it is better to be given before night sleep	-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. * Ranitidine is more potent; 150 mg can give the therapeutic effect, compared to 400 mg for cimetidine.	-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. -Endocrine effects (For Only Cimetidine) : • -increases in serum prolactin (Galactorrhea in women). • -Inhibits binding of dihydro-testosterone to androgen receptors (gynecomasteia –impotence). -All cross placenta & breast milk, should not be given in pregnancy unless it is necessary. ranitidine can be given to pregnant woman. - Inhbition of Cty p450 by Cimetidine. (potential toxicity from other drugs administered concomitantly). -Leukopenea and thrombocytobenia and headache with ranitidine(rare). -GIT disturbances (Nausea & Vomiting) -Bradycardia & hypotension (rapid I.V)
3- Proton pump inhibitors.: e.g: : Omeprazole ; Lansoprazole ; Pentoprazole ; Raprazole **Used In :** • Gastric and duodenal ulcer • (H.pylori Eradication) • Zollinger–Ellison syndrome. (1st) • GERD • NSAIDs associated ulcer • prevention of bleeding from stress-related gastritis. • PUD (4-8 weeks); faster & long- lasting ulcer relief.	• 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%).	-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.	-Headache. -Diarrhea. -Nausea. -decreased gastric acid secretion lead to hypergastrinemia 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.

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).(PPIs bid ,Clarithromycin, Amoxicillin)



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.

Questions

1. which one of these drug is a prodrug ?

   a. Famotidine b.Nizatidine c.Omeprazole

2. which one of these drug is first choice for Zollinger Ellison Syndrome ?

   a.Cimetidine b.Raprazole c.Ranitidine

3. which one of these drug we can't use it with warfarin?

   a.Nizatidine b.Cimetidine c.Ranitidine

   1-C 2-B 3-B

PHARMACOLOGY TEAM

Pharmacology leaders:
Tuqa Alkaff & Abullah Alanzi

Email:
pharmacologyteam1@gmail.com