Dr.Hanan
Week :

Drugs used in Rx of peptic ulcer

Definition:

- Stomach or duodenal lesion that occurs due to imbalance between aggressive factors and mucosal protective mechanisms

Aggressive factors:

1. pepsin
2. acid

Protective mechanisms:

1- PG E2- I2
2- mucus and bicarbonate
3- mucosal blood flow
4- so, rapid turnover of gastric mucosa

Risk factors:

1. H pylori infection
2. Alcohol
3. Smoking
4. Diet
5. Stress
6. Drugs: NSAIDS, corticosteroids, stress
7. Genetic factors
8. Diseases (Zollinger Ellison syndrome)
9. people with blood group O

➲Complications:

1) GI hemorrhage
2) pyloric stenosis
3) chronic iron diffeciency
4) Anemia
5) perforation

➲Symptoms:

1) NV
2) anorexia
3) upper abdominal pain
4) Weight loss
5) heart burn

➲Gastric secretion:

1) pepsinogens (chief cells)
2) HCL and intirinsic factors (parietal cells)
3) mucus ,bicarbonate(musuc secreting cells)

➲Regulation of gastric secretion:

1) histamine (local hormone)
2) Gastrin (hormone) *(inhibited by somatostatin)*
3) ACH (neurotransmitters)

🗣 Aims of Ulcer treatment:

1. symptoms relief of pain
2. promotion of ulcer healing
3. prevention of recurrence
4. prevention of complications

Drugs used in treatment of peptic ulcer

1. Gastric hypo-secretary drugs:
    a) H2 receptor blocker
    b) Anti histamine
    c) Proton Pump Inhibitors
2. Eradication of H pylori
3. mucosal cyto-protective agents
    a) sucralfate
    b) colloidal bismuth
    c) PG analogues
4. Neutralizing agents (antacids)

figure 1 ***

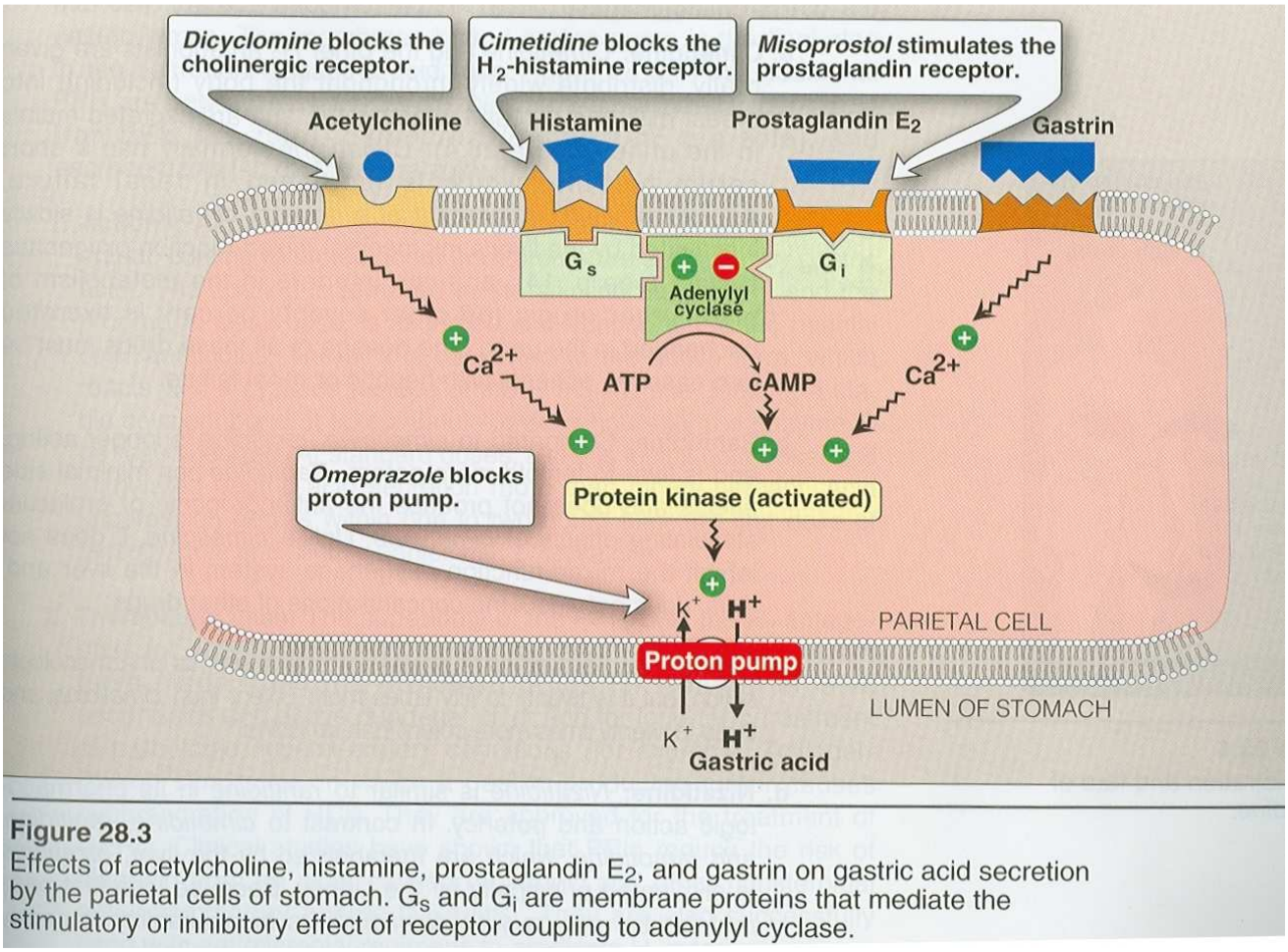

Figure 28.3
Effects of acetylcholine, histamine, prostaglandin E_2, and gastrin on gastric acid secretion by the parietal cells of stomach. G_s and G_i are membrane proteins that mediate the stimulatory or inhibitory effect of receptor coupling to adenylyl cyclase.

❶Gastric Hypo secretary agents:

- decrease gastric acid secretion >> promotion of healing and relieve the pain
- decrease absorption of keto kenazole and iron preparation ,digoxin
- they are subdivided into:
  a) anti muscarinics
  b) H2 receptor blockers
  c) PPIs

a) Anti cholinergic drugs:

1- non selective:

(**oxyphenonium –Dicyclomine**)

- decrease gastric motility
- delay gastric emptying → side effect
- cause heart burn (b/c they decrease motility → accumulation of food → increase Hcl)
- Atropin like side effects

2- selective Anti cholinergic :

(**pirenzepine – Telenzepine**)

- blocks M1 receptors in the parital cells
- selectivity in gastric acid secretion
- no effect on gastric acid secretion
- no effect on gastric motility
- no effect on CNS
- Dose: 50 Mg for 4-6 weeks
- uses:
  1. Adjuvant to H2 receptors blockers
  2. Decrease nocturnal pain in peptic ulcer

b) H2 receptor blockers:

- **Cimetidine**
- **Ramitedine**
- **Famotidine** (! Most potent)
- **Nizatidine**

🛠Mechanism of action :

- They competitively and reversibly bind to H2 receptor on the parietal cells

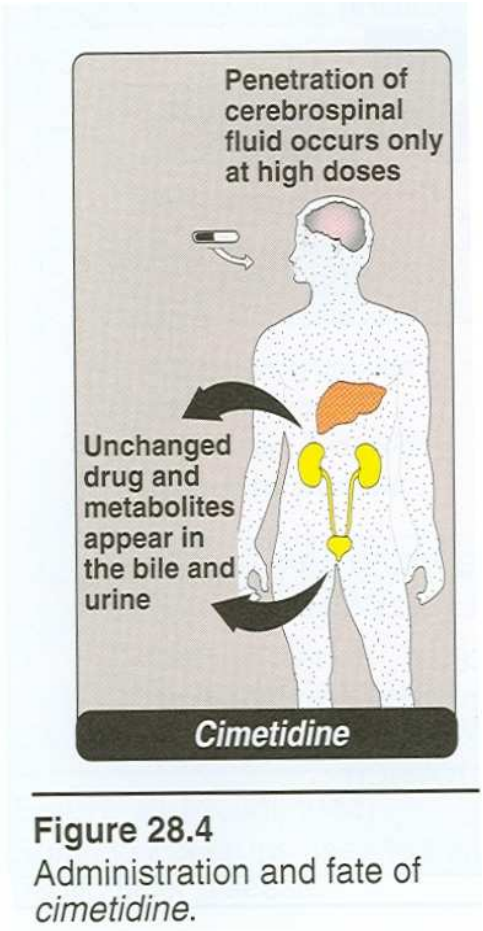

Figure 28.4
Administration and fate of *cimetidine*.

❖ Pharmacokinetics:

- Good oral absorption
- Plasma half life (1-3hr)
- Duration of action (4 – 12hr)
- 1st pass metabolism (50% EXCEPT Nizatidine 100% Bioavailability)
- Given before meals
- Metabolized by liver
- Excreted mainly in urine
- Cross placenta & excreted by milk

❖ Pharmacological action:

1. Reduce basal & foot stimulated.
2. Inhibit histamine, gastrin, and cholinergic drug induced secretions.
3. Reduce pepsin activity.
4. Promote mucosal healing & ↓ pain.

❖ Clinical Uses:

1. Duodenal ulcer (6-8 weeks)
2. Benign gastric ulcer (8-12 weeks)
3. Reflux esophagitis
4. Zollinger Ellison Syndrome (large dose)
5. Preanesthetic medication (to prevent aspiration pneumonitis)
6. Eradication of H pylori.

Adverse effects:

1. GIT disturbances: N& V
2. CNS effects (mainly with IV route): Headache , confusion , (elderly , renal or hepatic dysfunction)
3. Bradycardia & hypotension (in rapid I V So, we can't give it as bolus→we give it as slow IV infusion)
4. Endocrine effect (with cimetidine only)
   - ↑ in serum prolactine level.
   - Inhibit binding of dihydrotestosterone to androgen receptors.
   - Antiandrogenic action (gynecomastia, impotence)
   - Galactorrhea in women.
5. Cytochrome P450 inhibtion (cimetidine only) ↓ metabolism of oral anticoagulant(phenytoine , Thiophiline , BDZs).

Precautions:

- ✓ Maintains dose (b/c relapse may occur)
- ✓ Dose reduction in severe renal or hepatic failure & elderly.

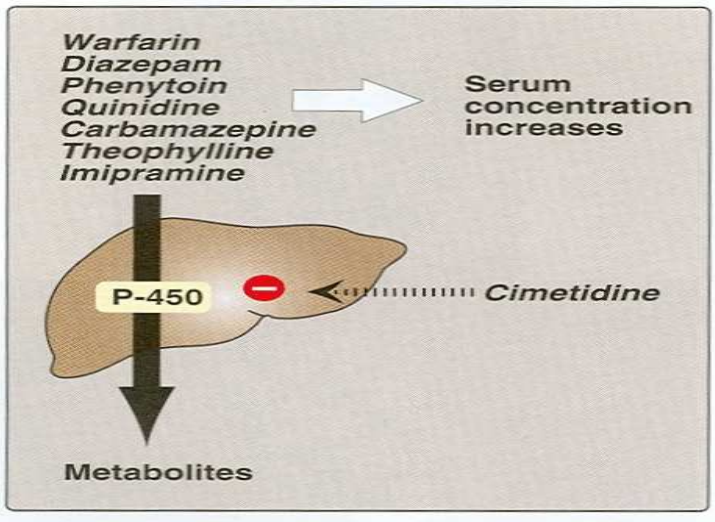

Figure 28.5
Drug interactions with *cimetidine*.

c) Proton pump inhibitors (PPIs) :

- **Omperazole**
- **Iansoprazole**
- **Pantoprazole**

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

Pharmacokinetics:

- All are :
  - prodrugs
  - taken orally

➲Are given as enteric coated capsules to protect them from destruction by acidity in gastric lumen.

- rapidly absorbed from the intestine.
- They are activated in the acidic medium of the secretory parietal cell canaliculus.

➲Inactivated if at neutral PH (combined with H2 receptor blockers)

- Have long duration of action =(12 - 24)hr
- Once daily dose is sufficient.
- Given 1 hr before meal.
- Bioavailability is reduced by food
- Are metabolized in the liver by CYTP450
- Dose reduction is required in severe liver failure
- Excreted in the bile
- Inhibit basal & stimulated acid secretion

✹They are more potent than H2receptor blockers.

❖ Clinical Uses: (1st choice in all of them)

1. Zollinger Ellison Syndrome (1st choice)
2. Resistance severe peptic ulcer (4-8 weeks).
3. Reflux esophagitis .
4. Eradication of H pylori.

Adverse effects:

1. GIT disturbances (N&V).
2. Achlorhydria – hypergastrinaemia
3. ↑ bacterial flora (Nitrosamine)
4. Gastric hyperplasia

❷Eradication of H-pylori

- ✓ H-pylori: Is a bacteria that causes chronic inflammation of the inner lining of the stomach.
  - Duodenal ulcer-Gastric ulcer.
  - Produce enzymes (tissue damage).
  - Risk factor for gastric cancer.
  - High acid content-inflammation-ulcer.
  - Eradication is important to prevent recurrence of ulcer.

➲Drugs:

- Bismuth compounds→ cytoprotective & bactericidal.
- Metronidazole
- Clarithromycine,tetracycline,amoxicillin. (antibiotics)
- Omperazole or H2 blockers.
- Resistance may develop to antibiotics.
- Combined therapy is used. → Triple or quadruple therapy.
- Better eradication is obtained using PPIs (omeperazole) &clarithromycine.
- Omeprazole used in exchange with bismuth or H2 blockers.

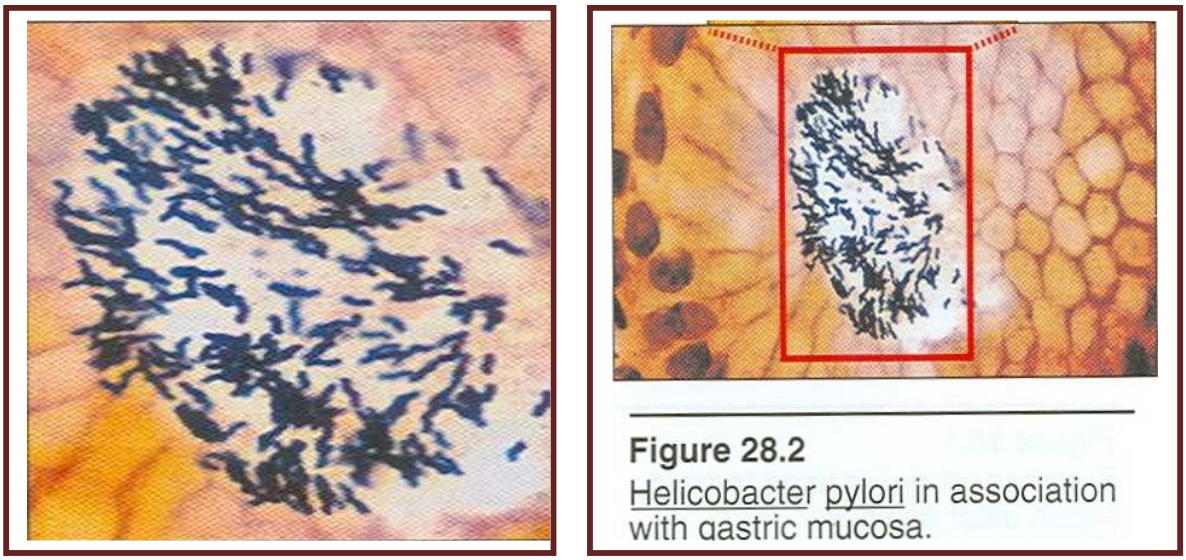

Figure 28.2
Helicobacter pylori in association with gastric mucosa.

❸ Mucosal protective agents

1) **sucralfate.**
2) **prostaglandine analogue.**
3) **colloidal bismuth**.

① Sucralfate :

✓ Sucrose octaphosphate + aluminium hydroxide

Mechanism of action:

1. In acidic PH,sucralfate dissociates into its components.
2. The negatively changed sucrose,octaphosphate binds with positively charged protein molecules found in damaged mucosa (coat over the ulcer).
3. Promote ulcer healing.→ so, it should not be systemically absorbed.
4. Inhibition of pepsin.→ through adsorption, coz it's not hyposecretory.
5. Stimulation of mucosal protective mechanisms (mucus & bicarbonates secretion).

Pharmacokinetics:

- Orally, poor systemic absorption.
- Duration (6h).
- Excreted in feces.
- Avoid co-administration of antacid or H2 blocker.
- Better taken on empty stomach.

Therapeutic uses:

- Benign gastric & duodenal ulcer.
- Chronic gastritis.

Adverse effects:

- Constipation & dry mouth.
- Interferes with absorption of some drugs (e.g. : tetracycline, theophylline, TCA).

② Misoprostol

✓ Prostaglandine analogue (PGE1).

- Decreases HCL secretion
- Promote tight junction of gastric cells → prevent back diffusion of HCL
- Increases mucus & bicarbonate secretion.
- Increases blood flow of mucosa ,improve healing of ulcer.

Pharmacokinetics:

- Orally
- T½= 30 min.
- Is converted into active metabolite.
- Excreted in urine - must be taken 3-4 times /day.

Therapeutic uses:

❖ Prevention of NSAIDs induced peptic ulcer :)

Adverse effects:

- Abdominal cramps (sever colicky pain).
- Diarrhea→ due to ↑ motility & secretion.
- Uterine contraction dysmenorrhea or abortion.
- Vaginal bleeding.

③Colloidal bismuth compounds:

✓ Colloid means high molecular wt → low absorption

- Bismuth substrate
- Tripotassium dicitrato bismutate

🛠Mechanism of Action:

- It forms a precipitate with mucous that cover the ulcer with a protective coat which prevents the effect of Hcl
- Promote healing of the ulcer
- Bactericidal effect against campylobacter pylori
- Decrease activity of pepsin
- Increase mucous & bicarbonate secretion
- ***No*** effect on Hcl

👽Adverse effects:

- Black stool (due to bismuth)
- Teeth discoloration
- Encephalopathy →in renal dysfunction (impaired execration)

Clinical Uses:

1) Triple therapy for eradication of H-pylori
2) Benign gastric & duodenal ulcer
3) Traveler's diarrhea

❹Drug that Neutralize Hcl: Antiacids:

- They are used to relief gastric pain associated with hypersecretion of Hcl
- They are subdivided into:

1. Systemic antacids
2. Nonsystemic antacids

❖ Mechanism Of action:

- Neutralization of Hcl
- Inhibition of pepsin (inactive @ PH=5)

❖ Clinical Uses:

- Relief gastric ulcer pain
- Dyspepsia

1)Systemic antacids

a) Sodiumbicarbonate

$NaHCo3 + Hcl \rightarrow NaCl + \underline{Co2*}$

☠Disadvantages:

- Rebound acidity
- Stomach distension due to Co2 libration →pain sensation
- Sodium load → salt & water retention (# in cardiac pts)
- Systemic alkalosis

b) Calcium carbonate:

$CaCo3 + Hcl \rightarrow Hcl3 + \underline{H2O*} + \underline{CO2*}$

Disadvantages:

- Libration of CO2 → stomach distention
- 10% is absorbed → hypercalcimia
- Rebound acidity
- Milk alkali syndrome (hypocalcaemia, renal failure b/c it precipitates in kidney → nephrocalcinosis)

الحياة حلوة بس نفهمها

2)Non - systemic antacids:

- Aluminum hydroxyl gel
- Magnesium trisilicate

$Al(oH)3 + Hcl \rightarrow Hcl3 + H2O$

Advantages:

- Longer duration of action
- Gradual neutralization of Hcl >> no rebound hyperacidity
- Adsorbs pepsin (b/c it contains Al)
- Minimal change in acid base balance
- No stomach distention

Disadvantages of :

✹ Al(oH)3:

- Constipation
- Drug interaction: decrease absorption of tetracycline, digoxin, & iron

✹ magnesium trisilicate:

- Diarrhea
- CNS depression (in renal failure pts)

➲they r given together b/c one causes constipation & the other causes diarrhea

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