Pharmacology

Drugs used in the gastrointestinal diseases

- **Gastro-esophageal reflux disease(GERD):** is the return of the stomach's contents back up into the esophagus. also known as reflex esophagitis and commonly called heartburn.is destroyed the mucus lined the esophagus due to reflux of gastric content to esophagus due to weakness of lower esophageal sphincter(LES) ,intraabdominal pressure, poor resistance of esophagus mucus to the acid.
- **Goal of therapy :**

1.reduce gastric acidity

2.reduce gastric volume

3. increase gastric empty

4.enhance the closure of LES

- **Treatment of heartburn**

1.antacids

2.alginates(Gaviscon)

3.H2 receptor antagonists(H2RAs)

4. Proton pump inhibitor (PPIs)

1. Antacids:

- containing AL salts AL (OH)2 ,Mg salts Mg(OH)2,Ca carbonate, Na bicarbonate

Are weak basic compounds that neutralize hydrochloric acid into the gastric secretion by **mechanism:-**

Weak base(antacid) + HCL =water and salt →decrease acidity ↑PH

Used in

Symptomatic management of gastro-intestinal disorders associated with gastric hyperacidity as

dyspepsia{ Dyspepsia Greek word (hard or difficult digestion)}, GERD, and peptic ulcer disease .

*Antacids provide immediate symptomatic relief for mild GERD and are often used in concurrently with other acid suppressing therapies.

*Best given when symptoms occur their duration short (30 min)on empty stomach, but duration extended 3 hr. when given with or within 1 hr. after a meal.

*rapid onset , short duration

Antacids:

AL hydroxide + Mg hydroxide

AL hydroxide + Mg hydroxide
+simethicone

Chewable tab Ca Carbonate + Mg Carbonate

Antacids:

Sodium bicarbonate+ citric acid
+tartaric acid

Sodium Carbonate+ citric acid

Antacids:

*antacids may be formulated with other active ingredient like Simethicon(anti gas)(Maalox plus)to control gas or alginic acid (Gaviscone)to act as physical barrier to acid.

Drug interaction:

- antacid can bind to concomitantly administered drugs and interfere with absorption of drugs (e.g.tetracycline and ciprofloxacin) because antacid chelate with antibiotic to form an insoluble inactive complex. So administration of ciprofloxacin 2hr before antacid.
- Antacid ↑PH of stomach, thus cause premature release of enteric coated tab in stomach rather than the intestine.

*Antacid in patient with renal failure should be avoided →antacid AL, Mg, small amount absorbed systemically and accumulate in body→ toxicity

Side effects:

AL- containing antacid tend to be constipating, Mg containing antacid tend to cause diarrhea. thus combination products of AL& Mg salts cause minimum bowel disturbances

Antacid containing Sodium bicarbonate should be avoided in patient if sodium intake should restricted(congestive heart failure ,hypertention)

Alginate

Alginate contain antacids form a sponge like matrix that float on the top of the stomach contents so when reflex occur alginate rather than acids will be reflexed &irritation is minimized ,protects the esophageal mucosa from acid attach.

Alginate preparations are also commonly combined with antacids to help neutralize stomach acid .

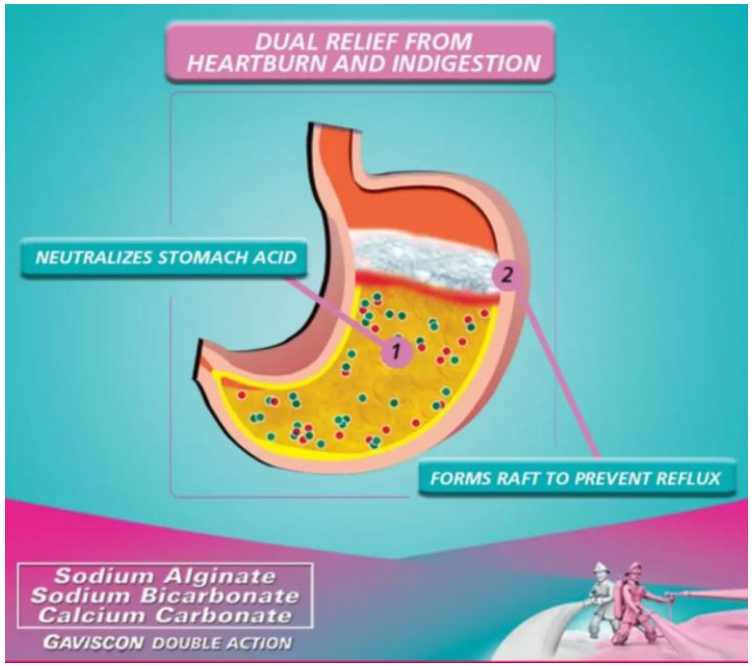
Gaviscon as suspension ,chewable tab. 10ml, 2-4 tab every 6 hr. after food

Used treat GERD, dyspepsia

Sodium alginate

NA bicarbonate

Ca bicarbonate



H2 Receptor Antagonists (H2RAs)

H2 receptor is one type of histamine receptor located in gastric mucosa ,which has excitatory effect, when histamine binding by H2 receptor increase the secretion of HCL.

H2RAs include: cimetidine, ranitidine, famotidine, nizatidine.

Uses:

GERD, gastric and duodenal ulcer , non-ulcer dyspepsia, prevention of bleeding from stress related gastritis.

*H2RAs competitively and selectively inhibit the action of histamine on the H2recepters of the parietal cells , thus reducing both basal and stimulated gastric acid secretion.

*Famotidine has the greatest potency, followed by nizatidine ,ranitidine, cimetidine.

H2RAs are taken on empty stomach(1hr before ameal)

They are remarkably safe and well tolerated the most common

H2 Receptor Antagonists

Cimitidine 200,400,tab, syrup,ampoule

Ranitidine 150,300 tab,syrup, ampoule

Famotidine,20,40 tab

H2 Receptor Antagonists (H2RAs)

adverse effects: headache ,somnolence, fatigue ,dizziness, constipation or diarrhea.

Cimetidine has weak anti androgenic effects, its use in high doses (hypersecretory conditions)has been associated with gynecomastia in men .this is reversible with discontinuation of medication or by switching to another H2RAs.

Cimetidine inhibits several CYP450 isoenzymes ,resulting in numerous drug interactions(theophylline ,warfarin, clopidogrel, phenytoin, propranolol)

Ranitidine less potential for hepatic CYP450 drug interaction

Famotidine, nizatidine do not interact with drugs metabolized by hepatic CYP450

PPI preferred are superior to H2RAs in reducing gastric acid secretion &mucosal healing. PPIs suppress gastric acid more strongly , for a longer period.

Proton Pump Inhibitors (PPIs)

PPIs are the most potent inhibitors of gastric acid secretion and include

Omeprazole, Lansoprazole,Rabeprazole,Pantoprazole,Esomeprazole,Dexlanzoprazole.

*PPIs block gastric acid secretion by inhibiting hydrogen potassium adenosine triphosphate(H-K ATPase)in gastric parietal cells ,which results in profound and long lasting anti-secretory effects.

*PPIs irreversibly inhibit proton pump H-K ATPase.

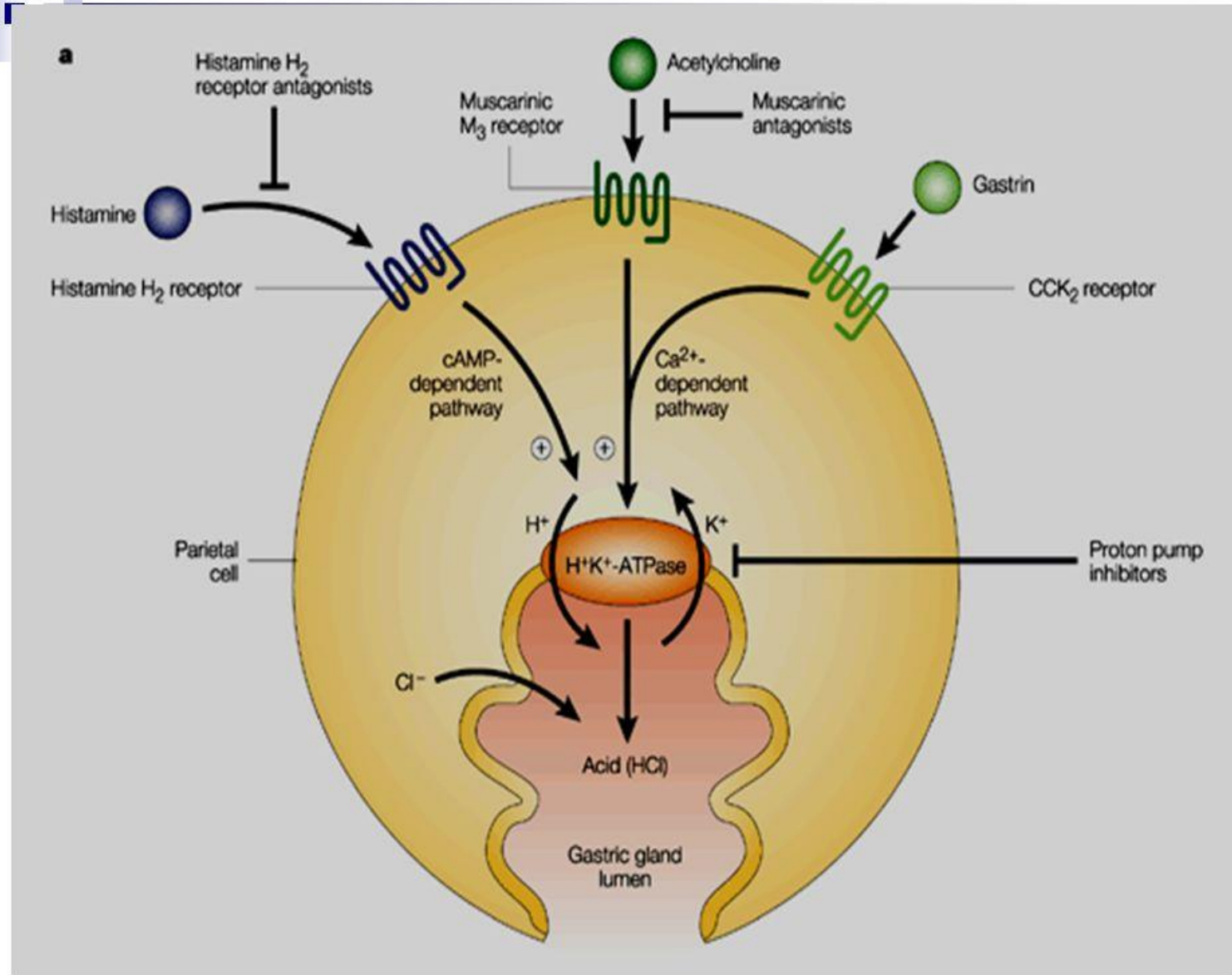
Uses

-Gastric and duodenal ulcer

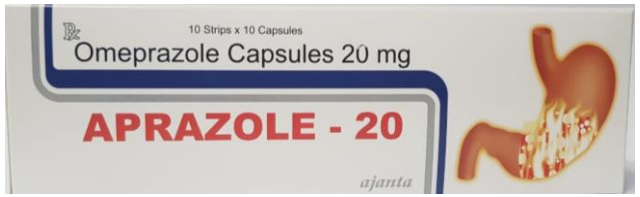
-In combination with antibacterial for the eradication of Helicobacter Pylori(abacteria that is common cause of ulcer)

-PPIs can be used in treatment of dyspepsia and GERD.

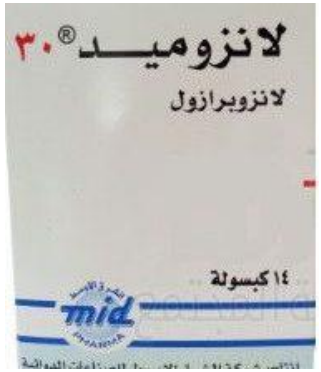
-prevention and treatment of NSAIDs-associated ulcers.


a
Histamine H_2 receptor antagonists
Acetylcholine
Muscarinic M_3 receptor
Muscarinic antagonists
Gastrin
Histamine
Histamine H_2 receptor
CCK_2 receptor
cAMP-dependent pathway
Ca^{2+}-dependent pathway
H^+
K^+
Parietal cell
H^+K^+-ATPase
Proton pump inhibitors
Cl^-
Acid (HCl)
Gastric gland lumen

Proton Pump Inhibitors



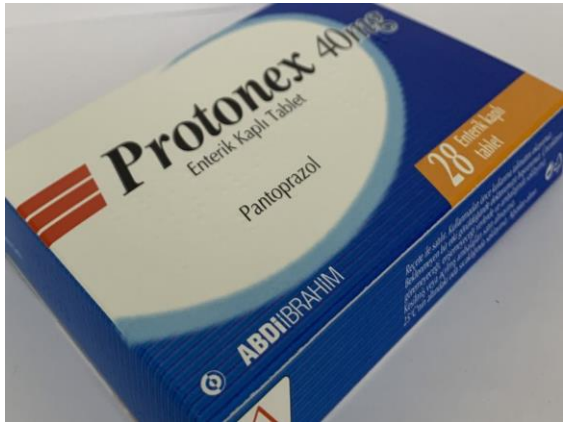
10,20,40,cap., vial



Lansoprazole
15,30 cap

Rabeprazole 10,20 tab

Proton Pump Inhibitors



Pantoprazole 20,40 tab

Esomeprazole 20,40 tab , vial

Proton Pump Inhibitors

PPIs given on empty stomach(food affects their absorption), they should be given 30-60 minute before food intake (once daily in the morning or may be twice daily one in the morning and the second in the at night.)

*PPIs→↓acid secretion 90 %

Adverse effects

- Headache ,dizziness, diarrhea , constipation ,nausea ,vit B12 deficiency.
- All PPIs can ↓absorption of drugs as ketoconazole, itraconazole that require acidic environment for absorption
- Esmoprazole ,omeprazole , lansoprazole reduce the antiplatelet effect of clopidogrel .
- Omeprazole may inhibit metabolism of clopidogrel, warfarin, diazepam, phenytoin
- Rabeprazole, pantoprazole have no significant drug interaction.

Promotility Agents or Prokinetic drugs

(**Prokinetic** agents) have significant potential clinical usefulness.

Agents that increase lower esophageal sphincter pressures may be useful for GERD.

Drugs that improve gastric emptying may be helpful for gastroparesis and postsurgical gastric emptying delay. constipation, heartburn, nausea, vomiting.

Metoclopramide & Domperidone

Metoclopramide and domperidone are dopamine D_2 receptor antagonists. Within the gastrointestinal tract activation of dopamine receptors inhibits cholinergic smooth muscle stimulation; blockade of this effect is believed to be the primary prokinetic mechanism of action of these agents.

These agents increase, increase lower esophageal sphincter pressure, and enhance gastric emptying .Metoclopramide and domperidone also block dopamine D_2 receptors in the chemoreceptor trigger zone of the medulla resulting in potent antinausea and antiemetic action

Metoclopramide & Domperidone

Clinical Uses

-Gastroesophageal Reflux Disease

-Impaired Gastric Emptying

-Non ulcer Dyspepsia

-Prevention of Vomiting

Adverse Effects

- The most common adverse effects of metoclopramide involve the central nervous system. Restlessness, drowsiness, insomnia, anxiety, and agitation occur in 10–20% of patients, especially the elderly.

Extrapyramidal effects (dystonias, akathisia, parkinsonian features) due to central dopamine receptor blockade occur acutely in 25% of patients given high doses and in 5% of patients receiving long-term therapy. sometimes irreversible, has developed in patients treated for a prolonged period with metoclopramide. For this reason, long-term use should be avoided unless absolutely necessary, especially in the elderly.

Elevated prolactin levels (caused by both metoclopramide and domperidone) can cause galactorrhea, gynecomastia.

- Domperidone is extremely well tolerated. Because it does not cross the blood-brain barrier to a significant degree, neuropsychiatric and extrapyramidal effects are rare.

Metoclopramide & Domperidone

Metoclopramide 5,10 tab, syrup,ampoule

Domperidone 10 mg tab

Mucosal Protective Agents

- The gastroduodenal mucosa has evolved a number of defense mechanisms to protect itself against the noxious effects of acid and pepsin.
- Both mucus and epithelial cell-cell tight junctions restrict back diffusion of acid and pepsin.
- Epithelial bicarbonate secretion establishes a pH gradient within the mucous layer in which the pH ranges from 7 at the mucosal surface to 1–2 in the gastric lumen.
- Blood flow carries bicarbonate and vital nutrients to surface cells.
- Mucosal prostaglandins appear to be important in stimulating mucus and bicarbonate secretion and mucosal blood flow. A number of agents that potentiate these mucosal defense mechanisms are available for the prevention and treatment of acid-peptic disorders.

1.Sucralfate

- Sucralfate is a salt of sucrose complexed to sulfated aluminum hydroxide. In water or acidic solutions it forms a viscous, tenacious paste that binds selectively to ulcers or erosions for up to 6 hours.
- It is also binds to proteins in the base of ulcers or erosion, forming a physical barrier that restricts further caustic damage and stimulates mucosal prostaglandin and bicarbonate secretion.
- Sucralfate used for prophylaxis of stress ulcer, Treat gastric ulcer.

Adverse effect :constipation

2.Prostaglandin Analogs

- The human gastrointestinal mucosa synthesizes a number of prostaglandins ,the primary ones are prostaglandins E and F. **Misoprostol,** a methyl analog of PGE1 , has been approved for gastrointestinal conditions. The serum half-life is less than 30 minutes; hence, it must be administered 3–4 times daily
- Misoprostol has both acid inhibitory and mucosal protective properties.
- It is believed to stimulate mucus and bicarbonate secretion and enhance mucosal blood flow. In addition, it binds to a prostaglandin receptor on parietal cells causing modest acid inhibition.

Clinical Uses

- It is approved for prevention of NSAID-induced ulcers in high-risk patients; however, misoprostol has never achieved widespread use owing to its high adverse-effect profile and need for multiple daily dosing.
- Proton pump inhibitors may be as effective as and better tolerated than misoprostol for this indication. Cyclooxygenase-2-selective NSAIDs, which may have less gastrointestinal toxicity .

Adverse Effects

-Diarrhea and cramping abdominal pain

-stimulates uterine contractions

3.Bismuth Compounds

Bismuth subsalicylate, containing bismuth and salicylate, and **bismuth subcitrate potassium**

Bismuth chelate with protein material in the ulcer base forming a coating to ulcers and erosions, creating a protective layer against acid and pepsin.. Bismuth compounds have direct antimicrobial activity against *H pylori.*

Clinical Uses

-Bismuth compounds are used in 4 drug regimens for the eradication of *H pylori* infection.

-For gastric and duodenal ulcer

Adverse Effects

Bismuth causes harmless blackening of the stool, darkening of the tongue,teeth.

Sucralfate tab (Gastrofait)

misoprostol (cytotic)

Bismuth subsalicylate

Peptic ulcer

Peptic ulcer :break in the gastric or duodenal mucosa that extend into deeper layers.

Due to imbalance between cell destructive(HCL, pepsin , H. Pylori infection, NSAID ingestion)and cell protective effects(mucosal blood flow, mucus, mucosal bicarbonate secretion).

Causes

-Helicobacter Pylori infection(60-90%)
-Chronic use of NSAIDs
-Stress related mucosal damage
-Smoking
-Zollinger-Ellison Syndrome(ZES)(↑gastrin hormone due to tumers→↑too much stomach acid)
-Genetic

Peptic ulcer

Many ways for healing and prevent recurrence of ulcer:

1.Reduction of acid secretion(H2RAs ,PPIs, antimuscarinic drug)

2.neutralization of secreted acid by antacid

3.enhancement of mucosal resistance: protecting the base of peptic ulcer (bismuth,sucralfate), Eradicating H-Pylori

4. cytoprotection(misoprostol)

Treatment of Eradicating H-Pylori:

1.For 14 days metronidazole and either (clarithromycin ,amoxycillin, or tetracycline)combined with suppression of acid secretion (omeprazole)

2.Bismuth, metronidazole, either (clarithromycin ,amoxycillin, or tetracycline)combined with (omeprazole) For 10-14 days.

Eradicating H-Pylori:

Clarithromycin

Tinidazole

lansoprazole

Bismuth subcitrate potassium

Metronidazole

tetracycline

THANK YOU