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# Gastrointestinal and Antiemetic Drugs

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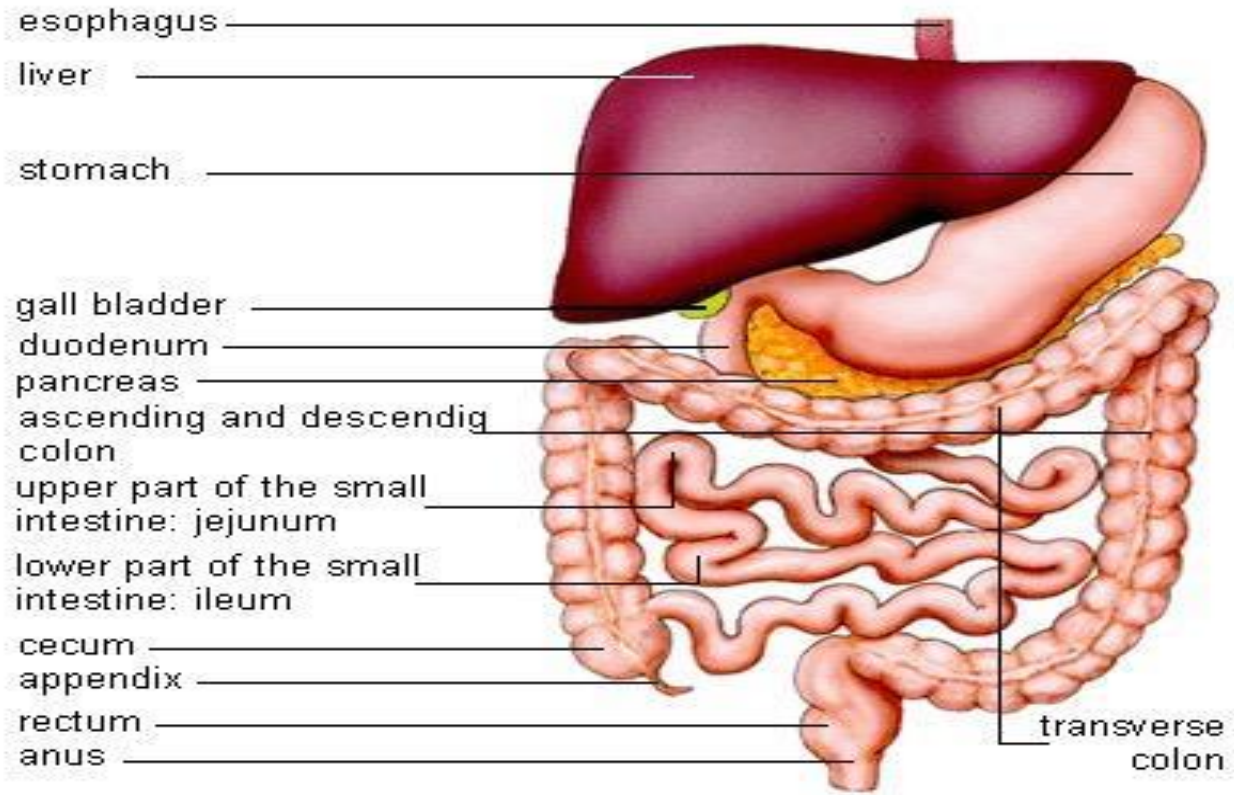


This chapter describes drugs used to treat six common medical conditions involving the gastrointestinal (GI) tract:

1) **Peptic ulcers and gastroesophageal reflux disease (GERD),**
2) **Chemotherapy-induced emesis.**
3) **Diarrhea.**
4) **Constipation.**
5) **Irritable bowel syndrome (IBS).**
6) **Inflammatory bowel disease (IBD).**

Other drugs are used almost exclusively to treat GI tract disorders. For example, H2 receptor antagonists and proton pump inhibitors (PPIs) are used to heal peptic ulcer.

## Peptic ulcer

The two main causes of peptic ulcer disease are infection with gram-negative **Helicobacter pylori** and the use of nonsteroidal anti-inflammatory drugs **(NSAIDs).**

Increased hydrochloric acid (HCl) secretion and inadequate mucosal defense against gastric acid also play a role.

**Treatment approaches** include

1) Eradicating the H. pylori infection.

2) Reducing secretion of gastric acid with the use of PPIs or H2 receptor antagonists, and/or

3) Providing agents that protect the gastric mucosa from damage, such as *misoprostol* and *sucralfate*.

**Figure 1** Summarizes agents that are effective in treating peptic ulcer disease.

# Peptic ulcer

- It is an ulceration of esophagus, stomach or duodenum.
- **Causes of peptic ulcer:**

 ↑ Secretion of HCl and pepsin.
 Helicobacter pylori. (70-90 %)
 ↓ Mucous and bicarbonate secretion.
 Drugs as NSAIDs and iron.
 High stress.
 Some diseases as Zollinger-Ellison syndrome.
 Smoking and alcohol.
 Spicy foods, tea, coffee and carbonated beverages.

## • Symptoms:

- Epigastric and abdominal pain.
- Nausea, vomiting and anorexia.
- Hemorrhage in severe cases.

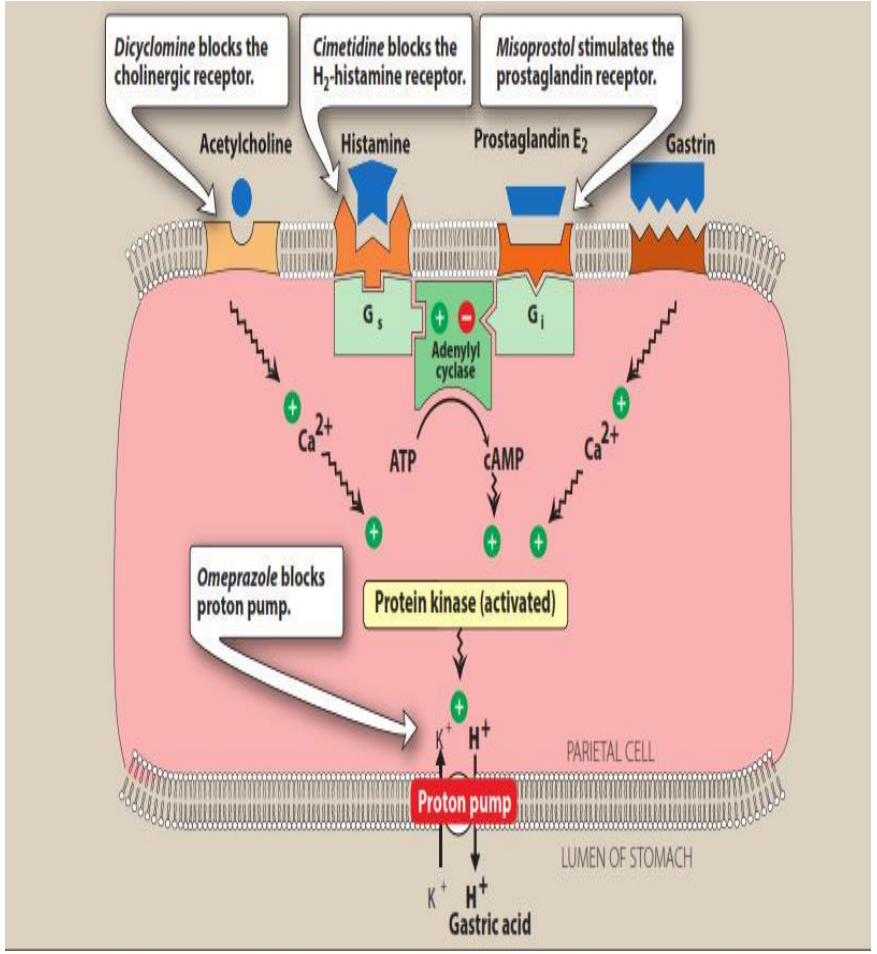
# • Treatments

- **The aims of treatment are to:**

 Relieve symptoms.

 Promote healing of ulcer.

 Prevent complications and recurrence.




**Effects of Ach, histamine, PG and gastrin on gastric acid secretion**

# Summary of drugs used to treat peptic ulcer disease.

**ANTIMICROBIAL AGENTS**

*Amoxicillin* GENERIC ONLY
Bismuth compounds PEPTO-BISMOL, KAOPECTATE
*Clarithromycin* BIAXIN
*Metronidazole* FLAGYL
*Tetracycline* GENERIC ONLY

**$H_2$ – HISTAMINE RECEPTOR BLOCKERS**

*Cimetidine* TAGAMET
*Famotidine* PEPCID
*Nizatidine* AXID
*Ranitidine* ZANTAC

**PROTON PUMP INHIBITORS**

*Dexlansoprazole* DEXILANT
*Esomeprazole* NEXIUM
*Lansoprazole* PREVACID
*Omeprazole* PRILOSEC
*Pantoprazole* PROTONIX
*Rabeprazole* ACIPHEX

**PROSTAGLANDINS**

*Misoprostol* CYTOTEC

**ANTIMUSCARINIC AGENTS**

*Dicyclomine* BENTYL

**ANTACIDS**

*Aluminum hydroxide* GENERIC ONLY
*Calcium carbonate* TUMS
*Magnesium hydroxide* MILK OF MAGNESIA
*Sodium bicarbonate* ALKA-SELTZER

**MUCOSAL PROTECTIVE AGENTS**

*Bismuth subsalicylate* PEPTO-BISMOL
*Sucralfate* CARAFATE

**1) Antacids:**

 Weak bases to neutralize gastric acidity.

 Inhibition of pepsin activity.

 Promote ulcer healing.

- Antacids given orally 1 – 3 hours after meals and at bedtime.

**- There are two types of antacids:**

**1- Systemic antacids (as NaHCO3):**

Soluble and absorbable → systemic alkalosis.

**2- Local antacids (other antacids):**

Insoluble and not absorbed → no systemic alkalosis.

## Sodium bicarbonate: (NaHCO3)

- Quick onset and short duration of action.
- Causes systemic alkalosis→ alkalization of urine:

→ Precipitate phosphate stones.

→ ↓ Excretion of weak basic drugs as ephedrine.

- Avoided in patients with hypertension or edema due to ↑ NaCl concentration.

## -Therapeutic uses:

 Peptic ulcer and heart burn.

 ↑ Excretion of weak acidic drugs as salicylates, sulfonamides and barbiturates → treatment the toxicity.

 In gout (↑ excretion of uric acid)

 Alkaline expectorant.

 In diabetic ketoacidosis.

 In urinary tract infections.

**Calcium carbonate: (CaCO3)**

- Has rapid onset and long duration of action.
- May cause constipation.

**Magnesium hydroxide: Mg(OH)2**

- Has delayed onset of action and long duration.
- Has laxative effect

**Aluminum hydroxide: Al(OH)3**

Causes constipation. (astringent)

**Magaldrate = Mg(OH)2 + Al(OH)3 →** synergism with less side effects.

- **Drug interactions:**

 Most antacids ↓ absorption of certain drugs as tetracycline, ranitidine, warfarin or quinolones → complex formation.

 Antacids → ↓ effect of sucralfate

## 2) Anti-secretory dugs:

## a- H2-blockers:

- Selective competitive blockers of histamine (H2) receptors on parietal cells of gastric mucosa → ↓ HCl and pepsin secretions.
- Reduce the effect of other substances that promote acid secretion as gastrin or acetylcholine.

**- Drugs:**

- **Cimetidine (Tagamet)®**

**(400mg bid or 800mg at bedtime).**

- **Rantidine (Zantac)®**

**(150mg bid or 300mg at bedtime)**

- **Famotidine (Pepcid)® (more potent)**

**(20mg bid or 40mg at bedtime)**

- **Nizatidine (Axid)®**

**(150mg bid or 300mg at bedtime)**

- **Pharmacokinetics**

After oral administration, the H2 receptor antagonists distribute widely throughout the body (including into breast milk and across the placenta) and are excreted mainly in the urine. *Cimetidine*, *ranitidine*, and *famotidine* are also available in intravenous formulations. The half-life of these agents may be increased in patients with renal dysfunction, and dosage adjustments are needed.

**- Therapeutic uses:**

 Peptic ulcer and heart burn.
 Reflux esophagitis.
 Zollinger-Ellison Syndrome.

- Cimetidine has been withdrawn in most countries due to androgenic side effects.

**b- Proton pump inhibitors:**

**- Mechanism of action:**

- Activated in the acid media → irreversible inhibition of H+/K+ ATPase → ↓secretion of H+ into the gastric lumen → maximal inhibition of HCl secretion.
- No effect on gastric motility.
- Longer duration of action than H2-blockers.

Examples:

**- Omeprazole: (Losec)®20-40 mg / day**

**- Lansoprazole: (Lanzor)®15-30 mg / day**

**- Rabeprazole: (Aciphex)® 20-40 mg / day**

**- Pantoprazole: (Controloc) 20-40 mg / day**

**- Esomeprazole: (Nexium)®20-40 mg / day**

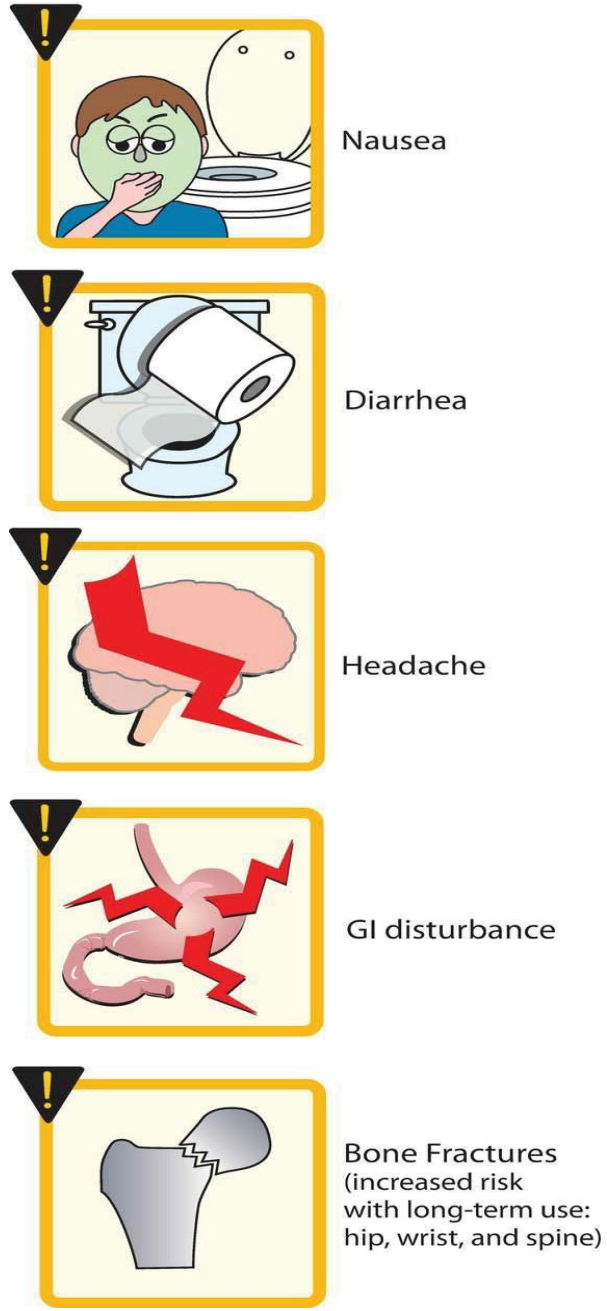
## - Therapeutic uses:

- Peptic ulcer and esophagitis.
- Gastroesophageal reflex disease (GERD)
- Zollinger-Ellison syndrome.
- Reduce the risk of ulcer bleeding caused by NSAIDs.

- Given orally before meals usually for short term therapy. (4-8 weeks)
- Also can be given parenterally.

## - Side effects:

- Headache, dizziness and drowsiness.
- Nausea, diarrhea.
- Skin rash.
- Chronic administration → ↓ absorption of vitamin B12. (need acidic media)




Some adverse effects of proton pump therapy

## - Drug interactions:

 Omeprazole (metabolic enzyme inhibitor) → ↓ metabolism of warfarin, phenytoin, diazepam and cyclosporine.

 ↓ Absorption of PH-dependent drugs as Ketoconazole.

- Long-term treatment with high doses may be carcinogenic. (in animal studies)

**c- Anti-muscarinic drugs:**

As: Pirenzepine (Gastrozepin)®

- Selective M1- antagonist.
- Dose: 50 mg bid orally for 4-6 weeks.
- Dry mouth, blurred vision and constipation are the main side effects.
- Not widely used, substituted by H2-blockers.

**d- Gastrin antagonists:**

As: Octreotide (Somatostatin)

- Analog for Growth Hormone Inhibitory Hormone.

→ ↓ release of gastric and pancreatic secretions.

- Given parenterally.
- Used mainly in gastric and pancreatic carcinoma.

**(3) Mucosal protective agents:**

- Enhance mucosal protection mechanisms → preventing mucosal injury, reducing inflammation and stimulate healing of ulcers.

**a- Sucralfate: (aluminum sucrose sulfate)**

- Forms complex with proteins of gastric mucosa → forming a paste coating the defect mucosa → prevent the degradation of mucous by HCl and pepsin → stimulate healing and prevent recurrence.
- Stimulates prostaglandin release.
- Increases mucous and bicarbonate production.

**Dose:**

**1g / 6 hours taken orally before meals and at bedtime.**

- Require acidic PH for activation, so it's not administrated simultaneously with H2-blockers, antacids or proton pump inhibitors.

**Side effects:**

 Dry mouth and constipation.  Indigestion.  ↓ Absorption of food.

**b- Colloidal bismuth compounds:**

**As: Bismuth subcitrate: (De-Nol)®**

**- Actions:**

 Selective binding to proteins of the ulcer → protection and promote healing.

 Has antimicrobial activity against H. pylori.

 ↑ Prostaglandin & mucous and ↓ pepsin production.

**- Dose:**

240 mg bid orally ½ hour before breakfast and at bedtime.

- May cause black color of oral cavity and feces.

**(4) Prostaglandines:**

**As:**

**Misoprostol: (Cytotic)®**

- Synthetic analog of PGE1.
- ↓ Secretion of HCl and ↑ Mucous and bicarbonate production → promote ulcer healing.
- Given orally 100-200 µg qid.

**- Side effects:**

 Nausea, diarrhea and abdominal pain.

 Fever & inflammation.

 Oxytocic → abortion. (contraindicated in pregnancy)

-N.B. Refer to Autacoids

- **Antibacterials against H. pylori:**

- H. pylori are gram -ve bacteria and present in about 70-90% of patients with peptic ulcer.
- For eradication of this infection use triple therapy or quadruple therapy.
- The common used antibacterials are:

**Clarithromycin: ( 500mg/12 hours)**
**Metronidazole: ( 400 mg/12 hours)**
**Or amoxicillin: (500 mg/ 12 hours)**
**Omeprazole : (20 mg/12 hours)**
**Or lansoprazole (15 mg/12 hours)**

**- Triple therapy for eradication of H. pylori:**

(**2 antibacterials** + PPIs)

PPI combined with amoxicillin (metronidazole may be used in penicillin-allergic patients) plus clarithromycin is a preferred treatment when rates of clarithromycin resistance are low and the patient has no prior exposure to macrolide antibiotics.

- **Quadruple therapy:**
- *bismuth subsalicylate*, *metronidazole*, and *tetracycline* plus a PPI is a recommended first-line option.
- This usually results in a 90% or greater eradication rate.

**(2 antibacterials + PPIs or H2 blockers + bismuth)**

- The combination taken for 2 weeks, then the treatment continues by antisecretory drugs (H2-blockers or PPIs) for 4-8 weeks.
- Administration of separated drugs is preferred than combination in one tablet.