Drugs used in the Treatment of Peptic Ulcer

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DRUGS USED IN THE TREATMENT OF PEPTIC ULCER

Acid peptic diseases include gastroesophageal reflux, peptic ulcer (gastric & duodenal) and stress related mucosal injury.
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<td>Epidermal growth factor &amp; transforming growth factor</td>
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Erosion or Mucosal ulceration occurs when the aggressive factors

\[ \text{Acid} \]
\[ \text{Pepsin} \quad \text{Overwhelm} \]
\[ \text{Bile} \]

the defensive factors (mucus, bicarbonate, PGS, blood flow and the process of regeneration after cellular injury)

99% of peptic ulcer is caused by the infection with Helicobacter pylori or by non-steroidal anti inflammatory drugs.
Drugs Used in the Treatment of Peptic Ulcer

Drugs is divided in to two groups.

- Agents that reduce intragastric acidity.
- Agents that promote mucosal defense.
Section VI / Drugs Affecting Gastrointestinal Function

![Diagram of gastric physiology and drug actions](image)

- **Gastrin**
  - Muscarinic antagonists
  - CCK2 antagonists

- **Histamine (H2)**
  - Muscarinic antagonists
  - CCK2 antagonists

- **EP3**
  - NSAIDs
  - Misoprostol

- **Superficial epithelial cell**
  - Muscarinic antagonists
  - Pirenzepine

- **Parietal cell**
  - K+ entry
  - Ca2+-dependent pathway
  - cAMP-dependent pathway

- **Proton pump inhibitors**
  - Proton pump inhibitors (X)

- **Antacids**
  - Antacids (X)
  - Bismuth metronidazole tetracycline clarithromycin amoxicillin

- **Sucralfate**
  - Sucralfate (X)
  - Carbenoxolone

- **Mucous Layer pH 7**
  - Gastric Lumen pH 2

- **HCO3-**
  - Mucus protection

- **H. pylori**
  - Clarithromycin amoxicillin
PHYSIOLOGY OF ACID SECRETION:

Parietal cell contains receptors for gastrin, histamine (H₂) acetylcholine (M₃)
When acetylcholine or gastrin bind to the parietal cell receptors & Cause increase in cytosolic calcium which in turn stimulates protein Kinases that simulate acid secretion from the proton pump (H+/K+ATPase) on the canalicular surface.
ANTACIDS: have been used for centuries in the treatment of patients with dyspepsia and acid peptic disorders. They were the mainstay of treatment for peptic ulcer disease until the advent of H2 receptor antagonists & Proton pump inhibitors. Still they are used for intermittent heart burn and dyspepsia.
MECHANISM OF ACTION:

Antacids are the weak bases react with gastric hydrochloric acid to form salt and water and reduce intragastric acidity. It also promotes mucosal defense mechanism of stimulation of mucosal PGS production.
After a meal approximately 45 Milli equivalents /hour HCL is secreted. A single dose of 156 milli equivalents of antacid given 1 hour after meal effectively neutralizes gastric acid up to 2 hours.
SYSTEMIC ANTACIDS

Sodium bicarbonate (baking soda):

It reacts rapidly with hydrochloric acid to produce carbon dioxide and sodium chloride. Formation of CO$_2$ results in gastric distention and belching. Unreacted alkali is readily absorbed and cause metabolic alkalosis when given in patients with renal insufficiency. Sodium Chloride absorption may exacerbate the fluid retention in patients with CHF, HT and renal insufficiency.
Calcium carbonate less soluble reacts more slowly than sodium bicarbonate with HCl to form Carbondioxide and calcium chloride. Like Sodium bicarbonate, Calcium Carbonate may cause belching or metabolic alkalosis. Calcium containing food along with Calcium Carbonate causes hyper calcemia, renal insufficiency & metabolic alkalosis. (Milk Alkali Syndrome)
NON SYSTEMIC ANTACIDS:

Formulations containing magnesium hydroxide or aluminium hydroxide react slowly with HCl to form magnesium chloride, aluminium chloride & water. No gas is generated. Belching & metabolic alkalosis does not occur. Unabsorbed magnesium cause osmotic diarrhoea and aluminium cause constipation. Both are given together to minimize the impact on bowel function. Patient with renal insufficiency should not take for long time.

Magnesium tricylicate and magnesium oxide are also used as antacids.
Alginic acid may be combined with an antacid to encourage adherence of the mixture to the mucosa, for reflux esophagitis.

Dimemeticone is sometimes included in antacid mixtures as an antifoaming agent to reduce flatulence. It is a silicone polymer that lowers surface tension and allows the small bubbles of froth to form into a large bubble that can be easily passed up from the stomach and down from the rectum.

Antacids + Oxethazaine (mucaine gel)
Antacids Interfere with The absorption of many drug therefore It should be given 2 hours after food (in between meals)

H2 RECEPTOR ANTAGONISTS:
Cimetidine
Ranitidine
Famotidine
Nizatidine
Roxatidine
**Pharmacodynamics**: H2 antagonists exhibit competitive inhibition at the parietal cell H2 receptors and suppress basal and meal stimulated acid secretion in a linear dose dependent fashion.
They are highly selective for \( H_2 \) receptor. Do not affect \( H_1 \) & \( H_3 \) receptors. The volume & gastric secretion and concentration of pepsin are reduced. \( H_2 \) antagonists reduce acid secretion stimulated by histamine, by gastrin & Cholinomimetic agents. Histamine produced by ECL cells by gastric or vagal stimulation is blocked by binding to the parietal \( H_2 \) receptors.

Inhibit nocturnal (90%) and day time acid secretion (60 – 80%)
USES:
Patient with heart burn or dyspepsia (GERD). Antacids followed by H₂ antagonist. Faster relief occurs with antacids. For heart burn the H₂ blocker should be administered twice a day. Peptic Ulcer, NSAIDs, PUD (can be used). Prevention of bleeding from stress induced ulcers.
I.V – H₂ antagonist.
SIDE EFFECTS:

Diarrhoea, headache, myalgia, constipation, fatigue, confusion, hallucination.

Cimetidine inhibits the metabolism of estradiol increase serum prolactin level and can cause gynaecomastia, impotence in men and galactorrhoea in women.

Pregnancy & Lactation: Should not be given, unless absolutely necessary, because it crosses placenta & secreted in milk.
H. PYLORI TREATMENT REGIMENS:
2 antibiotics + PPI for 10 – 14 days

Triple therapy

PPI – 20mg BD
Clarithromycin 500 mg – bd
Amoxicillin 1g – bd

If the Patient is allergic to penicillin, metronidazole 500mg bd. After completion of triple therapy, PPI should be continued for 4-6 weeks to ensure complete ulcer healing.
For patients with resistant infections quadruple therapy is recommended.

PPI + Amoxicillin + Clarithromycin + Bismuth sub citrate - 2 tablets 4 times daily.
Helicobactor pylori eradication therapy is:

- Indicated for gastric and duodenal ulcer not associated with NSAID use, and gastric lymphoma (especially MALT lymphoma),
- Not indicated for reflux oesophagitis and
- Equivocal in value for nonulcer dyspepsia, after incidental detection, and for prophylaxis of gastric cancer.
PROTON PUMP INHIBITORS PPI

- Prodrug
- Has high first pass metabolism
- Resemble H₂ antagonists in structure with complete different mechanism of action.
**MECHANISM OF ACTION:**

Irreversibly inhibits H+/K+ ATPase

Omeprazole is a racemic mixture of R – S – isomer.

Esomeprazole is the - S-isomer of omeprazole

Oral products are formulated for delayed release - as acid resistant enteric coated capsule or tablet formulation.
In case of Children capsule may be Dysfunction opened and the micro Enteral feeding granules can be mixed with orange juice

Omeprazole: Nonenteric coated powder. It can be administered via syringe or enteral tube. It should be administered in empty stomach.
Prodrug  ➔ Produce active reactive thiophillic sulfonamide cation reacts with H+/K+ ATPase enzyme by covalent disulfide linkage and irreversibly inactivate the enzyme. It inhibits the acid secretion for 24 hours. 18 hours are required to synthesize the new H+/K+ ATPase.
• Ideal Drug
• Short t1/2
• Well concentrated
• H+/K+ ATPase exist only in parietal cell.
• Long duration of action.
Clinical Uses:

- GERD
- H. pyloria
- NSAID
- Bleeding PU

Non Ulcer dyspepsia
Stress related mucosal bleeding, gastrinoma, Zollinger Ellison syndrome

Omeprazole 60 – 120 mg/day – before food
**Adverse Effects:**

Diarrhoea, headache, abdominal pain - 1-5%

Do not have teratogenicity

Safety during pregnancy not established. To release B\textsubscript{12} acid is required, with prolonged therapy minor B\textsubscript{12} deficiency can occur.

Nosocomial pneumonia, clostridium difficile infection.

Carcinoid tumors in rats

Long term PPI - Small benign gastric polyp reported but disappeared after stopping the drug.
**Pharmacokinetics:**
Metabolised by cyp450

**Drug Interaction:** Omeprazole inhibits the metabolism of Warfarin, diazepam and phenytoin

Rabeprazole and Pantoprazole have **NO Significant DI**

Esomeprazole decrease the diazepam metabolism

Lanzoprazole enhance the excretion of theophylline
Anticholinergics: Reduce of gastric juice & delay gastric emptying.

Pirenzepine: M1 receptor antagonist. It inhibits gastric secretion without producing typical atropinic side effects. The more likely site is intramural plexuses and ganglionic cells rather than the parietal cells themselves.
Oral bioavailability of pirenzepine is only 20 – 30% and penetration in brain is poor. It is primarily excreted unchanged in urine; t1/2 is 11 hours. It has been used safely in patients having glaucoma or prostatic hypertrophy. Contraindicated in reflux esophagitis because they aggravate by relaxing the lower esophageal sphincter.
**Ulcer protectives:**
Agent that promote mucosal defence:
SUCRALFATE
CBS – COLLOIDAL BISMUTH SUBCITRATE
PROSTAGLANDINS - MISOPROSTAL
**Sucralfate:**

The drug is a complex of sulfated sucrose and aluminium hydroxide in water (or) acidic solutions it forms a viscous tenacious paste that binds selectively to ulcers or erosion for up to 6 hours.

<3% is absorbed from the intestinal tract remainder is excreted in the faeces.
Pharmacodynamics:
Precise mechanism of action is unclear. It is believed that the negatively charged sucrose sulfate binds to positively charged proteins in the base of the ulcer or erosion and form a physical barrier that restricts further caustic damage and stimulates the mucosal prostaglandins and bicarbonate secretion.
Clinical Uses:

**Dose**: 1gm four times daily on empty stomach, atleast 1hour before meals. For prevention of Stress related bleeding decrease the incidence of GI bleeding in critically ill patients. No value the treatment of reflux esophagitis.
**Adverse Effects:**

**Constipation:** 2%, dryness of mouth rarely cause aluminium toxicity and hypophosphatemia

**C.I:** Renal insufficiency

**D.I:** It binds with other medications & impair their absorption.

**Prostaglandin analogs:**

PG – E, PGF – main PGS in GI mucosa.
**Misoprostal**: Methyl analog of PGE, following oral administration it is rapidly absorbed and metabolized to active free acid. Serum half life 30 minutes. Hence administered 3 - 4 times daily. It is excreted in urine.

**Pharmacodynamics**: Acid inhibitory and mucosal protective properties. Stimulate mucus and bicarbonate production.
Enhance mucosal blood flow. Binds with PGE receptor in the parietal cell and reduce histamine induced CAMP production & modest acid inhibition. It is very expensive.
**Other Actions:** Stimulate intestinal electrolyte and fluid secretion. cause Intestinal motility. Uterine contraction

Used in NSAIDs induced PUD
Adverse effects:
Diarrhoea, cramping abdominal pain in 10 – 20% patients.
Should not be administered during pregnancy or women of child bearing potential.
(PGE2(Enprostil, Arbaprostil, Rioprostil), given orally, produce similar effects.)
COLLOIDAL BISMUTH COMPOUNDS:

Bismuth sub salicylate → salicylate is absorbed & excreted in urine

Bismuth sub citrate

Bismuth dinitrate

99 % of Bismuth excreted in faeces

1% is absorbed from the intestinal tract

P.D: Bismuth coats ulcer and erosion

Stimulate Prostaglandins, mucous and bicarbonate secretion

B.S. Salicylate decrease stool frequency - Liquidity in acute infectious diarrhoea is reduced due to salicylate inhibition of intestinal PGS and chloride secretion.
• Has antimicrobial effects binds enterotoxins used in travelers diarrhoea
• Direct antimicrobial activity against H.pylori

Clinical Uses:
1. Acute diarrhoea
2. Traveler’s diarrhoea
3. MDR in H.pyloric infection (one of the component) Resistant infections.
Adverse Effects:

Cause blackening of stools – confused for G.I. bleeding - darkening of tongue prolonged use cause Bismuth toxicity resulting in encephalopathy ataxia, headache, confusion, seizures)

Not reported with BSS (or) citrate. Avoided in renal insufficiency patients
DRUGS TO BE AVOIDED

NSAID
Caffeine
Theophylline
Glucocorticoids
Iron
Alendronate
Non Pharmacological measures for GERD

• Elevate the head of the bed by 15 – 20 cm

• They should not lie down for 3 hours after a meal.

• Weight reduction

• Avoid tight garments, Large meals, alcohol, anti muscarinics Corticosteroids, NSAIDs, spicy/fatty food, chocolate, caffeine, smoking etc.,