Pharmacology summary

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Peptic ulcer

A defect in the lining of the stomach or the duodenum.

Causes of Peptic Ulcer:

Helicobacter pylori (most common), Drugs such as aspirin & other NSAIDs.

Other factors: Smoking, Stress, alcohol, **Zollinger Ellison syndrome (**a rare gastrin- secreting tumors.)

Treatment options: Reduce acid secretion, **Neutralize** acid in the lumen, **Protect** the mucosa from acid destruction, **Antibiotics** to eradicate Helicobacter pylori.

First group of drugs will be mentioned is **Neutralization of acid (Antacids):**

1) Aluminum antacids cause constipation

2) Magnesium antacids have laxative action; diarrhea.

3) Magnesium trisilicate

****Combination of Magnesium & aluminum antacids are most commonly used (No diarrhea or constipation).**

4) Calcium carbonate: associated with "acid rebound" with excessive chronic use, also, it may cause milk-alkali syndrome

5) Sodium bicarbonate: causes metabolic alkalosis.

Second group: H2-Receptor Antagonists:

Cimetidine, Ranitidine, Famotidine, Nizatidine. All of them have bioavailability equal to 50% except Nizatidine which has little first-pass metabolism.

These drugs inhibit 90% of **nocturnal acid** (depends on **histamine**) but have Modest impact on **meal-stimulated acid secretion** (which is stimulated by **gastrin, Ach and histamine**).

Clinical Uses:

1) Gastroesophageal Reflux Disease (GERD) 2) Non Ulcer Dyspepsia.

3) Prevention of Bleeding from Stress-Related Gastritis :**IV H2** antagonists are **preferable** over IV **PPI (proton pump inhibitor) in this case. (important to know)**

4) Peptic Ulcer Disease: replaced by PPI because H2-Receptor Antagonists are Not effective in the presence of H. pylori and not effective if NSAID is continued.

**** Cimetidine inhibits cytochrome P450 enzymes so can increase half life of many drugs.**

Third group is PPI : Omeprazole, Lanzoprazole, Esomeprazole Rabeprazole, Pantoprazole.

They are tablets with a pH-sensitive coating. **Prodrugs,** released in the intestine (Destroyed by acid).

Immediate-Release Omeprazole

contains **sodium bicarbonate** to protect the drug from acid degradation results in **rapid** response.

Active form covalently binds the **H+/K+ ATPase enzyme and **inactivates** it.

** **Inhibit both fasting & meal-stimulated acid secretion.**

Clinical Uses of (PPIs) :

1) Gastroesophageal Reflux (GERD): The **most effective** agents in all forms of GERD **(important to know)**

2) Nonulcer Dyspepsia: Modest activity.

3) Stress- Related Gastritis

4) Gastric acid hypersecretory states, including Zollinger -Ellison syndrome.

Usually high doses of **omeprazole** are used.

Important adverse effect of PPI is **reduction of cyanocobalamine absorption. (important to know)**

**triple therapy of H.pylori: PPI, Clarithromycin,(Amoxicillin or Metronidazole)

Fourth group: Agents that protect mucosa:

1) **sucralfate**: **physical barrier** that restricts further caustic damage and **stimulates** mucosal **prostaglandin** and **bicarbonate** secretion. Used in Prevention of **stress-related bleeding.**

2) **Prostaglandin Analogs: Misoprostol which is** methyl analog of **PGE1. Used in Prevention of NSAID-induced ulcers. (important to know)**

3) **Bismuth subsalicylate:** reduces stool frequency and liquidity in acute infectious diarrhea, used in treating **traveler's diarrhea**, used as second-line therapy for the eradication of H pylori infection, high doses result in **encephalopathy. (important to know)**

Drugs Stimulating GI Motility (Prokinetic agents)

1) **Cholinomimetic Agents:**

Bethanechol: Stimulates muscarinic **M3** receptors.

Prucalopride

Neostigmine: used in case of acute colonic pseudo-obstruction.

2) **Dopamine D2-receptor antagonists.**

Metoclopramide (cross BBB) & Domperidone (does not cross BBB). Mainly used in refractory heartburn, Gastroparesis.

****Metclopromide** crosses BBB so can cause parkinsonian features **(important**

****Domperidone** is used to promote postpartum lactation.

Laxatives: used in cases of constipation, many types:

1) Bulk-Forming Laxatives: one example is polycarbophil.

2) Stool Surfactant Agents (Softeners)

A) Docusate: Used in symptomatic treatment of **constipation & in painful anorectal conditions such as hemorrhoids and anal fissures**. **(important)**

B) **Glycerin suppository.**

3) Lubricant/Emollient:

Site of Action: **Colon.**

Liquid paraffin: Used to prevent and treat fecal impaction.

4) **Osmotic Laxatives: Nonabsorbable Sugars or Salts**

A) Magnesium hydroxide (milk of magnesia)

B) magnesium citrate & sodium phosphate: cause Purgation

C) Lactulose :**Disaccharide**, not absorbed causing retention of water through osmosis leading to softer, easier to pass stool.

Drug of choice in hepatic encephalopathy to trap NH3. **(important to know)

D) **Balanced Polyethylene Glycol:** used to clean the bowel before colonoscopy, a barium x-ray or other intestinal procedures.

5) **Stimulant Laxatives:** Direct stimulation of the enteric nervous system and colonic electrolyte and fluid secretion.

A) Anthraquinone Derivatives: Aloe, senna, and **cascara.** Occur naturally in plants.

leads to a brown pigmentation of the colon known as "melanosis coli**."

B) Bisacodyl

C)Phenolphthalein

D)Castor Oil

Prucalopride

6) Opioid Receptor Antagonists

A)**Methylnaltrexone:** Used for opioid induced constipation in patients with advanced illness not responding to other agents. **(important to know)**
B)**Alvimopan:** use for postoperative ileus in hospitalized patients.

Antidiarrheal Agents:

1) Opioid Agonists
Increase colonic transit time and fecal water absorption.
a) Loperamide
b) Diphenoxylate: Commercial preparations contain small amounts of **atropine (Lomotil)**

2) Bile Salt-Binding Resins
Cholestyramine ,Colestipol ,Colesevelam
Malabsorption of bile salts cause diarrhea. (Crohn's disease or after surgical resection),
They bind bile salts and decrease diarrhea.
Cholestyramine and **colestipol** **reduce** absorption of drugs and fat, but **Colesevelam** does **not**.

3) **Octreotide:**
actions similar to somatostatin. **Uses:**
Diarrhea due to vagotomy or dumping syndrome or short bowel syndrome or AIDS. **(important to know)**
Side effects: **Steatorrhea and formation of gallstones.**

Drugs Used in theTreatment of Irritable Bowel Syndrome(IBS):

1) Antispasmodics (Anticholinergics)
Dicyclomine and **Hyoscyamine** .
Block **muscarinic receptors** in the enteric plexus and on smooth muscle.

Alosetron
Potent & selective **antagonist of the 5-HT3 receptor**, Restricted to **women** with **severe diarrhea-predominant IBS** not responding to conventional therapies. **(important to know)**

Prucalopride

High-affinity 5-HT4 agonist. (important to know)

2) **Chloride Channel Activator**

Lubiprostone
PG analog stimulates type 2 chloride channel (ClC-2).
Approved for the treatment of women with IBS with predominant constipation. (important to know)

Antiemetic Agents

1) **Serotonin 5-HT3 Antagonists: Ondansetron, Granisetron.**
Block central 5-HT3 and peripheral (main effect) 5-HT3 receptors.

2) **Neurokinin** 1 **Receptor** (**NK1**) **Antagonists: Aprepitant**
Block central **NK1 receptors**. **(important to know)**
3) **Benzodiazepines**
Lorazepam
Diazepam
Reduce **anticipatory vomiting caused by anxiety**.

4) **H1 Antihistamines & Anticholinergic Drugs: Meclizine**
Used for the prevention of **motion sickness** and the treatment of **vertigo due to labyrinth dysfunction. (important to know)**

Drugs Used to Treat Inflammatory Bowel Disease (U**lcerative colitis** & **Crohn's disease)**
1) Aminosalicylates
5-aminosalicylic acid (5-ASA)
Aminosalicylates work topically (not systemically) in areas of diseased gastrointestinal mucosa.
Azo Compounds: Sulfasalazine, Balsalazide, Olsalazine :
5-ASA bound by an **azo (N=N) bond** to an inert compound or to another 5-ASA molecule.
In the terminal ileum and colon, resident bacteria cleave the azo bond by an **azoreductase enzyme**, releasing **5-ASA**.

Mesalamine Compounds: Pentasa :

Timed-release **microgranules** that release 5-ASA throughout the small intestine

Asacol :
5-ASA coated in a **pH-sensitive resin** that dissolves at the pH of the distal ileum and proximal colon).

Clinical Uses of 5-ASA:
5-ASA drugs are **first-line agents** for treatment of **mild to moderate** active **ulcerative colitis**. **(important to know)**
Their efficacy in Crohn's disease is unproven, although used as first-line therapy for **mild to moderate disease** involving the colon or distal ileum.
2) **Glucocorticoids: Prednisolone ,Hydrocortisone Budesonide**

Clinical Uses:
Moderate to severe active **IBD**. **Not useful for maintenance.**

3) **Antimetabolites: Azathioprim, 6-Mercaotopurine.**
Are **purine analogs**, **Immunosuppressants. (important to know)**
******Used in induction and maintenance of remission.

Methotrexate:
Mechanism of action:
Inhibition of dihydrofolate reductase enzyme **(important to know)**
Uses: Induction and maintenance of remissions of Crohn's Disease.

4) **Anti-Tumor Necrosis Factor Therapy**
Infliximab
Uses:
Moderate to severe **Crohn's disease, refractory ulcerative colitis.**
****** Therapy is associated with increased incidence of **respiratory infections; reactivation of TB. (important to know)**

Natalizumab
Humanized IgG4 monoclonal antibody.
Used for patients with **moderate to severe Crohn's disease who have failed other therapies.**

Pancreatic Enzyme Supplements:

Contain a mixture of **amylase, lipase, and proteases.**
Used to treat pancreatic enzyme insufficiency.
Example is Pancrelipase.

Drugs Used to Treat Variceal Hemorrhage:

Somatostatin, Octreotide, Vasopressin (Is a potent arterial vasoconstrictor)

Terlipressin is a vasopressin analog that have similar efficacy to vasopressin with fewer adverse effects.

Beta-Receptor-Blocking Drugs:
nonselective blockers such as **propranolol** and **nadolol** are more effective than selective β1 blockers in **reducing portal pressures** so used to treat **Variceal Hemorrhage.**

Amebiasis: is infection with **Entamoeba histolytica**. **This organism can cause:**
1) Asymptomatic intestinal infection.
2) Mild to moderate colitis.
3) Severe intestinal infection (dysentery).
4) Ameboma (a tumor-like mass in the intestines in amebiasis which results in a large local lesion of the bowel).
5) Liver abscess and other extraintestinal infection.

****Asymptomatic Intestinal Infection** treated with a **luminal amebicide**.(**Diloxanide furoate, Iodoquinol, and Paromomycin).**

Note that :
1)Diloxanide Furoate is the Drug of choice for **asymptomatic luminal infections. (important to know)**

2)Therapy with a luminal amebicide is also **required** in the treatment of **all** other forms of amebiasis.
3) **Paromomycin** is also used to treat **visceral leishmaniasis**
4) they are **not** Effective against **tissue trophozoites.**

****Amebic Colitis:**
Metronidazole + a luminal amebicide is the treatment of choice.

Dehydroemetine or emetine can also be used, but are best avoided because of toxicity.

Metronidazole
Drug of choice in the treatment of extraluminal amebiasis.
Tinidazole
Similar activity & better toxicity profile than metronidazole.

Clinical Uses: Metronidazole is the drug of choice in the treatment of:
Amebiasis, **Giardiasis** ,**Trichomoniasis. (important to know)**

Metronidazole has a **disulfiram -like effect. (important to know)

Emetine & Dehydroemetine
Effective against **tissue trophozoites** of E histolytica, their use is limited to **severe amebiasis when metronidazole cannot be used. (important to know)**

ANTHELMINTIC DRUGS

1) Albendazole:
Broad spectrum. Drug of choice for **hydatid disease** & **cystecercosis**.

****Inhibits microtubule synthesis** in nematodes that irreversibly impairs glucose uptake, intestinal parasites are immobilized and die slowly.
** cause **pancytopenia** (low level of all blood cells produced by the bone marrow).

2) **Mebendazole:** inhibits microtubule synthesis, irreversibly impairs glucose uptake. Intestinal parasites are immobilized & die slowly.
kills hook worm, pin worm , ascariasis and trichuriasis.

3) **Pyrantel Pamoate: A neuromuscular blocker (important to know)**
highly effective for **pinworm, ascaris** & **Trichostrongylus orientalis** infections and moderately effective against **hookworm**.

4) **Piperazine**
Only recommended for the treatment of **ascariasis**.

5) Niclosamide: salicylamide derivative.
Used for the treatment of most tapeworm infections.
Adult worms (but not ova) are rapidly killed, due to inhibition of oxidative phosphorylation or stimulation of ATPase activity. **(important to know)**

6) Diethylcarbamazine Citrate (important to know)
Drug of choice for **filariasis**, **Loa loa** & **tropical eosinophillia**
**** Leukocytosis** is common as adverse effect.

7) Doxycycline
Has **macrofilaricidal** activity against **Wuchereria bancrofti** (lymphatic filariasis)

8) Ivermectin: A GABA agonists Paralyzes nematodes,**drug of choice** for the treatment of **onchocerciasis** (river blindness) and for **strongyloidiasis. (important to know)**

9) Bithionol
The drug of choice in the treatment of **sheep liver fluke** (Fasciola hepatica) and the **second drug of choice** in lung fluke (Paragonimus westermani).

10) Praziquantel
Effective in **schistosome infections,**
Neurocysticercosis is an adverse effect.

11) Metrifonate: alternative drug for **Schistosoma haematobium** infections.
Not active against S mansoni or S japonicum.
**** it is an Organophosphatecholinesterase inhibitor**

12) Oxamniquine
Alternative to praziquantel for the treatment of **S mansoni** infections.
Used extensively for mass treatment.
Not effective against S haematobium or S japonicum.