CHAPTER 7

DRUGS USED IN GASTROINTESTINAL DISEASES

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INTRODUCTION

Peptic ulcer, reflux esophagitis, gastroparesis, constipation, Diarrhoea, inflammatory illnesses, Zollinger-Ellison syndrome, and infections are common GIT disorders. Most of them are pharmacologically treatable. This chapter discusses different drugs used for the treatment of these GIT disorders. However, anti-infective drugs will be discussed in another chapter.

DRUGS USED IN ACID-PEPTIC DISEASE:

Stomach ulcers (gastric and duodenal), gastroesophageal reflux, and Zollinger-Ellison syndrome are all examples of acid-peptic illness. Peptic ulcer disease is believed to be caused by an imbalance between the cell-destructive effects of hydrochloric acid and pepsin on the one hand and the cell-protective actions of mucus and bicarbonate on the other. Proteolytic enzyme, pepsin is activated in gastric acid that may digest the stomach wall. It causes eruption of stomach wall that leads to ulcer formation. Helicobacter pylori, a Gram-negative and spiral-shaped bacterium, is also play an important role in ulcer pathogenesis. In gastroesophageal reflux, gastric fluid enters the esophagus that cause heartburn or other symptoms like indigestion, dyspepsia, pyrosis, and so on. Zollinger-Ellison syndrome is caused by a pancreatic tumour that produces too much gastrin, which promotes stomach acid output.

Acid-peptic disorders can be treated by drugs, which are able to:

A. Gastric acid Neutralizers (Antacids) e.g. magnesium hydroxide
B. Gastric acid secretion inhibitors (H_2 Blockers) e.g. cimetidine
C. Enhance mucosal defences (Mucosal protectives) e.g. sucralfate
D. Antimicrobial action against H. pylori (Antibiotics) e.g. clarithromycin

Ulcer's successful treatment strategy is founded on the aphorism “No Acid, No Ulcer"

Anti-ulcer drugs reduce cell-destructive effects, improve cell-protective actions, or both in the prevention and treatment of peptic ulcer disease.

A. Gastric acid neutralizers (Antacids):

Antacids are weak bases (alkaline compounds) that neutralize stomach acid (hydrochloric acid).

In the stomach, Antacids combine with hydrochloric acid to form neutral or less acidic or poorly absorbed salts and raise the PH of stomach secretion; above a pH of 4,

pepsin is also become inactive. There are two types of antacids: systemic and nonsystemic.

Systemic antacids, such as sodium bicarbonate, are absorbed into bodily fluids and may change acid-base balance. It is effective in treating metabolic acidosis.

Non-systemic antacids have no substantial effect on acid-base balance. They are used as stomach antacids and comprise aluminium, magnesium, and calcium compounds, for example. ($Al(OH)_3$, $CaCO_3$, $Mg(OH)_2$).

- Gastric antacids differ in potency, onset of action, duration of action, and side effects.
- Magnesium containing antacids relatively have high neutralizing capacity, rapid onset of action, but cause diarrhoea and hypermagnesemia.
- Aluminium containing antacids generally have a low neutralizing capacity, slow onset of action but long duration of action. However, these may cause constipation.
- Calcium-based antacids are also equally effective and have a rapid onset of action. But, these are rarely used in peptic ulcer disease because these type of antacids associated with acid hypersecretion (acid-rebound) and milk-alkali syndrome.

Most of the gastric antacids work chemically, while some, such as magnesium trisiolicate, can also work physically. Aluminium hydroxide and magnesium hydroxide combinations (e.g. Gelusil, Maalox etc) are the most often used antacids.

B. Antisecretory drugs (Gastric acid secretion inhibitors):

Parietal cells present on the gastric mucosa secreted hydrochloric acid through H^+K^+-ATPase proton pump. Parietal cells contain various receptors such as acetylcholine, histamine and gastrin that control H^+K^+-ATPase proton pump. Stimulation of H^+K^+-ATPase proton pump controls the HCl secretion. Antagonists of acetylcholine, histamine and gastrin inhibit HCl secretion as shown in Fig 6.1.

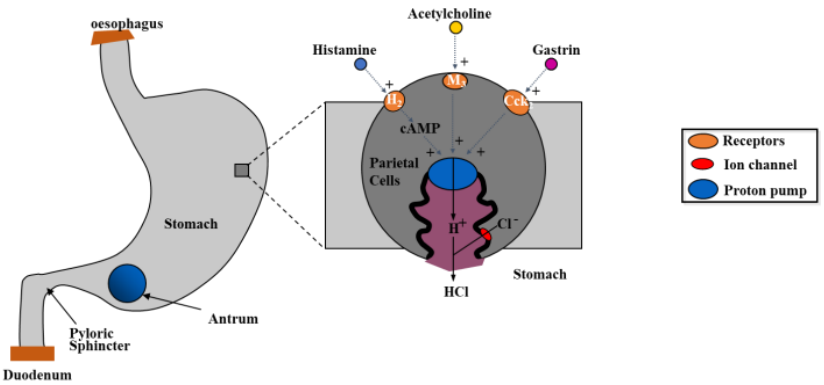

Fig 6.1: Release of gastric acid is promoted by acetylcholine, gastrin and histamine.

Antisecretory drugs include H_2-receptors blockers, Proton pump inhibitors (PPI) and Anticholinergic agents

H_2-receptors blockers: Cimetidine, ranitidine, famotidine, nizatidine are few of the **c**ommonly marketed H_2-receptors blocking agents. Cimetidine is the prototype drug of the H_2-receptors antagonist class of drugs.

Cimetidine dosage: For prophylaxis of recurrent ulcer**,** PO 400mg 2 times/day, with meals and at bed time, or 800mg once daily at bed time for 6-8 weeks is used. For the treatment of Zollinger-Ellison syndrome PO 400mg at bed time is used.

Adverse effects: Common adverse effects are muscular pain, headache, dizziness. At high dose cimetidine also show anti-androgenic effects like impotence, gynecomastia, menstrual irregularities, etc.

Drug interaction: Cimetidine is act as cytochrome P450 (CYP) inhibitors. When Cimetidine is co-administered with warfarin, theophylline, phenytoin, etc. Its leads to drug-drug interactions. Blood concentration of the latter drugs is increase that leads to increase in their biological effects.

Proton pump inhibitors: Omeprazole, lansoprazole, pantoprazole are commonly marketed drugs as H^+K^+-ATPase proton pump inhibitors. This class of drugs inhibit H^+-K^+-ATPase proton pump that is involved in terminal step of acid secretion to release H^+ into the gastric lumen.

Omeprazole dosage: For the treatment of gastritis, gastroesophageal reflux disease, PO 20mg/day for 4-8 weeks is used. For the treatment of Zollinger-Ellison Syndrome, PO 60mg once daily used. For peptic ulcer disease, PO 10-60mg/day is used.

Adverse effects: Common adverse effects of Omeprazole are headache, Diarrhoea and nausea.

Anticholinergic agents: Pirenzepine, dicyclomine are commonly marketed drugs as anticholinergic agents. This class of drugs mainly use in prevention and treatment of peptic ulcer disease, Zollinger Ellison syndrome, reflux esophagitis. Anticholinergic drugs are not used alone for the treatment of peptic ulcer. However, anticholinergic drug can be used in combination of other antiulcer drugs like H_2-antagonists, antacids, etc. when anticholinergic agents is used with antacids, acid neutralizing effects prolong due to delay gastric emptying. anticholinergic agents can also be used with any anti-ulcer drug if antispasmodic effect (to relieve abdominal pain) needed.

C. Cytoprotective (Mucosal Protective) Agents:

Cytoprotective agents are act locally by forming a protective layer between the ulcers and gastric juice (gastric acid, pepsin, and bile salts). Formation of protective layer prevent the direct exposure of stomach mucosa to gastric juice without altering the secretion of gastric acid. Commonly used cytoprotective agents are sucralfate and colloid bismuth compounds (Tripotassiu and Dicitratobismuthate).

- Colloidal bismuth compounds are also bactericidal against H. pylori. Antibiotics such as clarithromycin, amoxicillin, metronidazole, and tetracycline are also used in combination of cytoprotective agents to eradicate H. pylori in ulcer treatment.
- Other class of mucosal protective agents are prostaglandins that also have additional antisecretory. Misoprostol is marketed prostaglandin used for prevention of NSAID – induced ulcer.

LAXATIVES AND CATHARTICS (PURGATIVES)

Drugs that are used orally to promote bowel evacuation are called Laxatives and cathartics.

Laxative has mild effects and helps in elimination of soft formed stool while cathartic has strong effects and helps in elimination of liquid or semi liquid stool. Both laxative and cathartics are used interchangeably since the effects are determined by the dosage rather than the substance itself. For examples castor oil shows laxative effect if consumed 4ml and cathartic effect if consumed 15-60 ml. Based on mode of action laxative and cathartics are classified as bulk forming laxatives, osmotic laxatives, Stimulant (irritant) laxatives, fecal softeners, and lubricant laxatives.

Bulk forming laxatives: Substances that are unabsorbed from the intestine are included in this category. Hydrophilic colloids like psyllium, bran, methylcellulose, etc. have high water holding and swelling capacity. When mixed with water, the materials expand and form gel, increasing the volume of the faecal matter and stimulating peristalsis and defecation.

Osmotic laxatives: These compounds are not adequately absorbed, resulting in a greater than typical solution in the colon, causing water retention. This increase in pressure and volume in colon that causes stimulation of peristalsis. Magnesium sulfate, magnesium hydroxide, sodium phosphate, etc. are belong to this class of laxatives.

Stimulant (irritant) laxatives (cathartics): These types of laxatives are the most potent and abused used laxatives, working by irritating the GI mucosa and drawing water into the gut lumen. This result in feces is moved too rapidly and watery stool is eliminated as a result. Castor oil, bisacodyl, phenolphthalein, cascara sagrada, glycerine, etc. are few of the commonly used stimulant laxatives. Amongst them glycerine can be administered rectally as suppository.

Fecal softeners: These types of laxatives allow water to enter into stool by reducing the surface tension of the fecal mass and also decrease water absorption through intestinal wall. Docusate one of the fecal softeners has detergent like property.

Lubricant laxatives: These type of act through two mechanisms. One, by softening the stool by decreasing the colonic absorption of fecal water and secondly, by lubricating the intestinal wall. Most commonly used lubricant laxatives is liquid paraffin (mineral oil). Its is used as retention enema.

Laxatives and cathartics are used in following indications:

1. Constipation is a major condition among the elderly, and laxatives are often or excessively used. Non-drug strategies to avoid constipation (e.g., increasing fluid and high-fiber food consumption, exercise) are far preferable than laxatives.
2. Stool softeners are used to alleviate constipation in those who should avoid straining during stool movements due to heart disorders, haemorrhoids, and other issues. They soften faeces, making them simpler to pass.
3. Saline or stimulants are used to empty intestine during major surgery, during preparation of bowel surgery or diagnostic procedures.
4. Saline or stimulants are also used to enhance the elimination of toxic substances from the GIT.

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5. Saline or stimulants are also used to enhance enhance excretion of parasite like tapeworm, etc. after administration of anthelmintic drugs.

ANTIDIARRHOEAL

The drugs used for the treatment of diarrhoea are categorized under antidiarrhoeal agents. Diarrhoea is a medical disorder characterized by the frequent ejection of liquid or semi-liquid stools, which impairs fluid and electrolyte absorption. In most cases, medication intervention is not necessary since it is a defensive mechanism utilized by the body to flush out the offending bacteria or substance. Antidiarrhoeal medications can be used to relieve symptoms (non-specific therapy) or to address the underlying cause of the condition (specific therapy). Non-specific therapy includes use of opiates and opiate derivatives, adsorbent-demulcent agents, and anticholinergic agents for mild diarrhoea. However, Non-specific therapy not recommended in infectious diarrhoea.

Opiates and opiate derivatives are the most effective for symptomatic diarrhoea therapy. They reduce diarrhoea by decreasing the propulsive motions of the small and large intestines. Diphenoxylate and loperamide are most commonly used opiate derivatives for the treatment of diarrhoea. Morphine is effective but not used because of serious potential adverse effects,

Adsorbent-demulcent products, such as kaolin–pectin based preparation, may be used as antidiarrhoeal agents; however, if administered concurrently, they may adsorbed nutrients and other medications, including antidiarrhoeal agents.

Anticholinergic drugs, such as atropine, are occasionally used to relieve stomach cramping and discomfort caused by diarrhoea.

Specific therapy includes use of antibiotics such as ampicillin, chloramphenicol, colistin, co-trimoxazole etc. for the treatment of severe or prolonged diarrhoea (>2-3 days) due to infection cause by salmonella, shigella, campylobacter and clostridia. Specific therapy is recommended for use in carefully selected cases of bacterial enteritis, only when specific causes have been determined.

Oral rehydration therapy that contains glucose-electrolyte solution should be given in severe or prolonged diarrhoea cases as an electrolyte and fluid replacement. It contains combination of glucose (20 gm), NaCl (3.5 gm), $NaHCO_3$ (2.5 gm), and KCl (1.5 gm) for 1000 mL water.

ANTIEMETICS

Drugs that are used for the prevention and treatment of nausea and vomiting categorized as antiemetics. Nausea is an uncomfortable sense of stomach discomfort followed by a desire to vomit. Vomiting is the oral expulsion of stomach contents. Although nausea and vomiting can occur alone, the two symptoms are most commonly seen combined. Vomiting occurs when the vomiting centre in the medulla oblongata is activated. Dopamine and acetylcholine are important stimulators of the vomiting centre. To some extent, vomiting is a defensive mechanism that can be triggered by a variety of irritating stimuli. Most antiemetic drugs work by affecting the vomiting centre, CTZ, cerebral cortex, vestibular system, or a combination of these. Antiemetic medications are often more successful in prevention than in therapy. Drugs used to treat nausea and vomiting belongs to various therapeutic categories. Antiemetic drugs include:

Chlorpromazine, a phenothiazines (neuroleptics) derivative, is one of the drugs that is useful in preventing or treating nausea and vomiting induced by drugs, radiation treatment, surgery, and other stimuli. Its act on CTZ and vomiting center in the medulla oblongata by blocking dopamine receptors. Chlorpromazine generally not effective in motion sickness.

Antihistamines, such as promothazine and dimehydrinate, are particularly useful in the prevention and treatment of motion sickness. However, they may cause concurrent drowsiness that may be troublesome for travelers. Scopolamine, another anticholinergic drug, is particularly helpful in relieving nausea and vomiting caused by motion sickness.

Serotonin antagonist (5-HT3 receptors), such as Ondansetron, is useful to prevent chemotherapy, radiation therapy, and surgery induced vomiting and nausea. It acts by inhibiting the effect of serotonin, a naturally occurring chemical that can trigger nausea and vomiting.

Metoclopramide is also an antiemetic that has both central and peripheral antiemetic actions. Centrally, metoclopramide inhibits dopamine activity. Peripherally, metoclopramide enhances the release of acetylcholine, which accelerates the pace of stomach emptying (also used in esophapeal reflux)

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DRUGS USED TO INDUCE VOMITING

In the case of noncorrosive poisoning, and assuming that incomplete absorption of the toxin has occurred, vomiting can be induced. The medicine used for this is emetine, which is the active component of ipecacuanha (syrup of ipecac). Emetine causes CTZ by directly irritating the upper intestine and acting on absorption.

DRUGS USED IN THE TREATMENT OF HAEMORRHOIDS

Haemorrhoids are varicose veins of the anal canal that can be quite painful for the sufferer. There is no pharmacological treatment for this condition, which is usually self-limiting but may require surgical intervention. However, the usage of medications may alleviate the pain. Antihaemmorhoidal preparations contain one or more of following agents.

1. Stool softeners may help with constipation by reducing straining, which can aggravate the disease.
2. Local anesthetics such as lignocaine and benzocaine also relieve pain.
3. Corticosteroids such as predniosolone suppress inflammation, itching and swelling.
4. Vasoconstrictors such as adrenaline and phenylephine decrease the venous swelling.
5. Astringent compounds such as tannic acid reduce swelling by precipitating cell surface proteins.

DRUGS USED IN INFLAMMATORY BOWEL DISEASE (ULCERATIVE COLITIS AND CROHN'S DISEASE)

Both Ulcerative Colitis and Crohn's Disease are autoimmune inflammatory disorder. Crohn's disease can affect the whole intestine, whereas ulcerative colitis affects the rectum and colon. Both conditions can cause stomach pain and discomfort. The objective of treating inflammatory bowel disease is to decrease the inflammation that causes your signs and symptoms. There are various class of drugs used to treat these disorders. One is use of corticosteroids such as prednisolone and other is sulphonamides drugs such as.

Anti-inflammatory drugs are frequently used as the first line of therapy for inflammatory bowel disease. Corticosteroids and aminosalicylates, such as mesalamine,

sulfasalazine, balsalazide and olsalazine, are commonly used anti-inflammatory drugs. The medicine you take is determined by the region of your colon that is impacted.

Immunosuppressant drugs are also used for the treatment of therapy for inflammatory bowel disease. These drugs function in a number of ways to suppress the immunological response, which causes the body to generate inflammatory chemicals. Inflammatory chemicals responsible for damaging the lining of the digestive tract. Commonly used immunosuppressant drugs are azathioprine, mercaptopurine and methotrexate.

Antibiotics

Antibiotics may be used in combination with other therapies or when infection is a risk, such as in cases of perianal Crohn's disease.

Antibiotics may be used in addition to other medications or when infection is a concern-in cases of perianal Crohn's disease, for example. Ciprofloxacin and metronidazole are two often prescribed antibiotics.

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