UNIT 10 DRUGS ACTING ON GASTROINTESTINAL TRACT SYSTEM

Structure

10.1 INTRODUCTION

Gastro-intestinal system is a long tube through which food passes. It commences at the mouth and terminates at the anus. There are various groups of drugs acting on GIT at different levels and exerts their pharmacological and clinical actions.

Objectives

After studying this unit, you should be able to:

- understand the different drugs used as laxatives in the treatment of constipation;
- mechanism of action and therapeutic uses of the different drug classes;
- groups of drugs used in the treatment of diarrhoea; and
- different drugs used in peptic ulcer.

10.2 LAXATIVES

These are the drugs which promote the evacuation of bowels and used in constipation.

10.2.1 Bulk Forming Agents

These contain natural or semisynthetic hydrophilic colloidal derivatives of cellulose. These drugs act to increase the volume of stool by absorbing water and as a result softening of faeces occurs. These are safe drugs (except in patient with strictures when intestinal obstruction may be precipitated. Therefore not used in these conditions). Adequate hydration of the patient is to be maintained. The onset of action occurs in 12-24 hours after oral intake.

10.2.2 Osmotic Laxatives

These solutes are not absorbed in intestine. They retain water osmotically in bowel lumen and distend the bowel, thereby increasing peristalsis indirectly. These agents should be administered with plenty of water. The administration of sodium salts is to be avoided in patients of cardiac failure, renal failure and hepatic failure.

Lactulose is a semisynthetic disaccharide of fructose and lactose. It is not digested or absorbed in small intestine thereby withdrawing water into bowel lumen. It breaks down in colon to form more osmotically active products. It is also used in hepatic coma patients to reduce the absorption of ammonia from the colon.

10.2.3 Stool Softener

Liquid Paraffin is a petroleum hydrocarbon, an inert viscous liquid. It is a faecal softener and causes lubrication. It is indicated in postoperative constipation.

Docusate is an anionic detergent which softens the stool by water accumulation in intestinal lumen and emulsifies the colon contents. It is indicated in obstetric, habitual, geriatric, paediatric constipation or when straining is to be avoided (recent myocardial infarction, severe hypertension, post-operative cases, abdominal hernia), fissures, haemorrhoids and bed ridden patients.

10.2.4 Stimulant Laxatives

These drugs exert their laxative action by increasing motility of colon. Colicky pain may occur and on the long term use may lead to hypokalemia. These drugs are to be avoided in pregnancy and children.

Bisacodyl is stimulant laxative, when administered orally or as a rectal suppository it produces increased peristalsis by direct action on the mucosa of the colon, usually resulting in a soft formed stool. It is indicated in all forms of constipation.

Senna is not active as such but after oral intake when it reaches colon, the bacteria liberate the active form. Active form acts on myenteric plexus to increase peristalsis. It also inhibits salt and water absorption in colon. It is indicated in intestinal evacuation for radiological examination and atonic constipation.

SAQ 1

a) Bulk forming agents are not used in patients with _____.

b) _____ laxatives are to be avoided in pregnancy and lactation.

c) _____ is also used to reduce ammonia in hepatic coma patients.

10.3 ANTIDIARRHOEAL AGENTS

Diarrhoea is defined as frequent passage of liquid faeces with or without blood and mucus. It occurs due to various causes, infective or non-infective.

Antidiarrhoeals are given for symptomatic relief of diarrhoea. The first step in treatment of acute diarrhoea is replacement of fluid and electrolytes. If due to diarrhoea there is severe dehydration, it requires immediate hospitalisation for intravenous fluid and electrolyte replacement. Antidiarrhoeal drugs are administered for obtaining symptomatic relief in acute diarrhoea but have untoward effects. Along with antidiarrhoeal drugs, antispasmodics are administered in those patients who have diarrhoea with abdominal pain. They are classified as given in the following subsections.

10.3.1 Absorbents and Bulk Forming Drugs

They are colloidal bulk forming agents which swell by absorbing water. They modify the consistency and frequency of stools. They are used for functional bowel disease associated with diarrhoea. They are safe substances but their effect occurs slowly over a period of few days.

10.3.2 Antimotility and Antisecretory Drugs

Antimotility drugs are opioid drugs. They increase small bowel smooth muscle tone and segmentation activity. They also reduce propulsive movements and decrease intestinal secretions while increasing absorption.

Loperamide has a direct action on intestinal musculature and having a weak anticholinergic property. It is used to treat acute and chronic diarrhoea. **Diphenoxylate** is an opioid. It is used in acute and chronic diarrhoea but since it crosses the blood brain barrier it can cause CNS effect similar to opioids. Atropine is added with diphenoxylate to discourage abuse. **Sulphasalazine** is an antisecretory drug inhibits locally prostaglandin synthesis, decreases mucosal secretion. It is used in rheumatoid arthritis and ulcerative colitis. Side effects include fever, rashes, blood dyscrasias, nausea, vomiting and headache.

10.3.3 Antimicrobial Therapy

Antimicrobials have a limited role in treatment of diarrhoea because only a small percentage of diarrhoeas are caused by bacterial infection. Majority of cases are due to non infective causes. Antimicrobial therapy has no role in Rotavirus and food poisoning. Specific antimicrobial drugs are discussed in the unit titled 'Chemotherapeutic agents'.

SAQ 2

a) First step in treatment of acute diarrhoea is replacement of _____ and _____.

b) _____ is added with diphenoxylate to discourage abuse.

c) _____ is 5-aminosalicylic acid linked with sulfapyridine through an azo bond.

10.4 ANTIULCER AGENTS

Peptic ulcers are chronic, most often solitary lesions that occur in any part of GIT exposed to the aggressive action of acid and peptic juices.

Duodenal ulcer patients have an increased capacity to secrete acid and pepsin, increased responsiveness to stimuli of acid secretion and more rapid gastric emptying.

Gastric ulcer patients have a low to normal levels of gastric acid, but never true achlorhydria. Some primary defect in gastric mucosal resistance is seen and also an increased tendency to back diffusion of H^+ ion. Other influences are thought to be decreased production of bicarbonate buffer, decreased blood flow which permits acid ions to accumulate.

The various drugs used in peptic ulcer are as under:

10.4.1 Hydrogen Receptor Antagonists

The hydrogen (H_2) antagonists in clinical use are analogs of histamine that competitively inhibit the interaction of histamine with H_2 receptors and are highly selective. They inhibit gastric acid secretion elicited by histamine and other H_2 agonists in a dose dependent manner. H_2 blockers are used in the treatment of:

- Duodenal ulcer
- Gastric ulcer
- Zollinger-Ellison syndrome (ZES)
- Gastroesophageal reflux
- NSAIDs induced ulcers
- Prophylaxis of aspiration pneumonia

10.4.2 Proton Pump Inhibitor

Omeprazole is the prototype member of the gastric proton pump inhibitors (PPIs) which reduces gastric acid secretion. They have a quick onset of action and effective control of gastric acid secretion is achieved with once daily dosing. Proton pump inhibitors are indicated in:

- Treatment of duodenal ulcer.
- Treatment of gastric ulcer.
- Treatment of reflux oesophagitis.
- For control of acid secretion in patients of Zollinger-Ellison syndrome.

10.4.3 Prostaglandin Analogues

PGE_2 and PGI_2 are the main prostaglandins synthesised by the gastric mucosa. They decrease acid secretion and improve mucosal defense mechanism.

The important use of prostaglandin analogues is in arthritic patients who are on chronic use of NSAIDs and are not responding to H_2 receptor antagonists.

10.4.4 Ulcer Healing Drugs

Carbenoxolone sodium is a derivative of glycyrrhizic acid (obtained from liquorice) and has been found to be effective in healing both gastric and duodenal ulcer without affecting volume or acidity of gastric juice.

10.4.5 Ulcer Protective Agents

Sucralfate is the aluminium salt of sulfated sucrose. It polymerises at pH < 4 to form a sticky, viscid yellow-white gel which adheres to ulcer base. The gel acts as a strong mechanical barrier because of a strong electrostatic interaction of the drug with proteins at ulcer site. It also has antibacterial activity.

It precipitates surface proteins at ulcer base and acts as a physical barrier, preventing acid, pepsin and bile from coming in contact with ulcer base. It also augments gastric mucosal PG synthesis thereby enhancing protective action. It has no acid neutralising action. It promotes healing of both gastric and duodenal ulcers and also prevents ulcer recurrence.

10.4.6 Antacids

Antacids are basic compounds that neutralise acid in gastric lumen, have no effect on gastric acid secretion. They are quantitatively compared in terms of their **acid neutralising capacity** (ANC), which is defined as the quantity of 1 N HCl (in mEq) that can be brought to pH 3.5 in 15 minutes by a unit dose of antacid preparation. An ideal antacid should be potent in neutralizing acid, inexpensive, not absorbed from GIT and contain negligible amounts of sodium, should be sufficiently palatable to be readily tolerated with repeated dosage and should be free of side effects. An ideal antacid is yet to be developed. Role of antacids in the treatment of peptic ulcer is:

1. Primary pain relief.
2. Higher dose given continuously can promote ulcer healing.
3. Are superior to H_2 blockers in bleeding peptic ulcer.

Systemic Antacids

Systemic antacids e.g. sodium carbonate is water soluble and potent neutralizer, but is not suitable for the treatment of peptic ulcer because of risk of ulcer perforation due to production of carbon dioxide in the stomach. Systemic absorption lead to alkalosis, may worsen edema and CHF because of increased Na^+ load.

Non-Systemic Antacids

They are insoluble and poorly absorbed compounds. **Magnesium carbonate** reacts with hydrochloric acid at a slow rate. **Magnesium hydroxide** reacts with hydrochloric acid promptly. **Magnesium trisilicate** has the property to adsorb and inactivate pepsin and to protect the ulcer base. **Aluminium Hydroxide is a** weak and slow reacting antacid. The aluminium ion relaxes smooth muscles, thus delays gastric emptying and causes constipation. It can also adsorb pepsin at pH > 3 but releases it at lower pH. **Magaldrate** is a hydrated complex of hydroxy magnesium aluminate. It initially reacts with acid and releases $Al(OH)_3$ which then reacts more slowly. It is a good antacid, with both prompt and sustained acid neutralizing action. **Calcium Carbonate** is a potent antacid with rapid acid neutralizing capacity, but on long term use, it can cause hypercalcemia, hypercalciuria and formation of calcium stones in the kidney.

SAQ 3

a) Fill in the blanks with appropriate words:

   i) The _____antagonist can decrease gastric acid secretion.

   ii) _____ is a ulcer healing compound derived from glycyrrhizic acid.

   iii) _____ is a hydrated complex of hydroxy magnesium aluminate.

b) What are antacids?

10.5 SUMMARY

Peptic ulcers are chronic, most often solitary lesions that occur in any part of GIT exposed to the aggressive action of acid and peptic juices.

- Laxatives are the drugs which promote the evacuation of bowels and used in constipation.
- Bulk forming agents increase the volume of stool by absorbing water and as a result softening of faeces occurs.
- Antimotility agents increase small bowel smooth muscle tone and segmentation activity. They also reduce propulsive movements and decrease intestinal secretions while increasing absorption.

- Majority of cases of diarrhoea are due to non infective causes, and therefore, antimicrobial therapy has no role in them.
- H2 antagonists inhibit gastric acid secretion by food and fundic distension and also inhibit fasting and nocturnal acid secretion.
- PPIs effectively inhibit both basal and stimulated acid secretion irrespective of the stimulus.
- Prostaglandins decrease acid secretion and improve mucosal defence mechanism by increasing mucous and bicarbonate production.
- Antacids are basic compounds that neutralise acid in gastric lumen, have no effect on gastric acid secretion.

10.6 TERMINAL QUESTIONS

1. What do you understand by the term "laxative"? Classify laxatives.
2. What are the main therapeutic uses of laxatives?
3. What are antimotility and antisecretory drugs?
4. What are PPIs?
5. What is ANC (acid neutralising capacity)?
6. What are H_2 receptor blockers?

10.7 ANSWERS

Self Assessment Questions

1. a) Strictures b) Stimulant c) Lactulose
2. a) Fluid, electrolytes b) Atropine c) Sulfasalazine
3. a) H_2 receptor
   b) Carbenoxolone sodium
   c) Magaldrate
   d) Antacids are basic compounds that neutralise acid in gastric lumen, have no effect on gastric acid secretion.

Terminal Questions

1. These are the drugs which promote the evacuation of bowels and used in the management of constipation. They can be classified as follows:

   I. **Bulk forming agents**
   II. **Osmotic laxatives**

III. **Stool softener**
IV. **Stimulant laxatives**

2. Laxatives are indicated in obstetric, habitual, geriatric, paediatric constipation or when straining is to be avoided (recent myocardial infarction, severe hypertension, post-operative cases, abdominal hernia), fissures, haemorrhoids, bed ridden patients, bowel clearance before radiography, endoscopy, labour or surgery.

3. Antimotility drugs are opioid drugs. They increase small bowel smooth muscle tone and segmentation activity. They also reduce propulsive movements and decrease intestinal secretions while increasing absorption. They mediate these actions through opioid μ receptors. Antisecretory drugs are those drugs which reduce the intestinal secretions, as a result they reduce the volume of intestinal contents thus reducing the peristalsis. The drugs in these categories are as follows:

   Loperamide: An antimotility drug, it has direct action on intestinal musculature and having a weak anticholinergic property. It is used to treat acute and chronic diarrhoea. Adverse effects include abdominal cramps and skin rash.

   Diphenoxylate: It is another antimotility drug which is chemically an opioid. It is used in acute and chronic diarrhoea.

   Sulfasalazine: It is an antisecretory drug that inhibits local prostaglandin synthesis and decreases mucosal secretion. It is used in rheumatoid arthritis and ulcerative colitis. Side effects include fever, rashes, blood dyscrasias, nausea, vomiting and headache. Other drugs in this category are **mesalazine, olsalazine and balsalazine**.

4. PPIs, or Proton Pump Inhibitors are drugs that reduce the gastric acid secretion and are indicated in the treatment of duodenal ulcer, gastric ulcer, reflux oesophagitis and Zollinger-Ellison syndrome.

5. ANC stands for Acid Neutralizing Capacity. It is a quantitative measure of the efficacy of an antacid preparation. It is defined as the quantity of 1 N HCl (in MEq) that can be brought to pH 3.5 in 15 minutes by a unit dose of antacid preparation.

6. H_2 receptor blockers are one of the most important group of drugs used in the treatment of peptic ulcers. They are analogs of histamine that competitively inhibit the interaction of histamine with H_2 receptors and are highly selective. They inhibit gastric acid secretion elicited by histamine and other H_2 agonists in a dose dependent manner. The clinically used H_2 receptor blockers are cimetidine, ranitidine, famotidine, etc. They are indicated in the treatment of duodenal ulcer, gastric ulcer, Zollinger-Ellison syndrome, gastroesophageal reflux disease, NSAIDs induced ulcers and prophylaxis of aspiration pneumonia.