PHARMACOLOGY OF GIT

3rd Year Pharmacology and Toxicology- Biomedical Sciences
School of Health Sciences UNZA

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- *Overview of GIT pathophysiology*
- *Pharmacotherapy of peptic ulcer & gastro-oesophageal reflux disease, vomiting & vertigo, diarrhoeal ,Irritable bowel syndrome & inflammatory bowel disease*

LEARNING OBJECTIVES

By the end of the lectures, students should be able to :

- *Identify common disorders of the gastrointestinal tract (GIT)*
- *Describe treatment strategies for common disorders of the GIT.*
- *Identify the classification of drugs used to treat common disorders of the GIT*
- *For each of the drug classes , know representative drug examples, explain their mechanism of action, primary actions, important adverse effects,drug interactions and contraindications.*

INTRODUCTION

GIT responsible for:

- *Providing the body with essential nutrients*
- *Maintaining adequate levels of all essential nutrients in the bloodstream to facilitate normal activity*
- *Eliminating wastes derived from the diet, and some products of the body's metabolism, in order to avoid toxic waste inside the body.*

THE DIGESTIVE SYSTEM

- *Consists of two basic anatomic divisions: Alimentary canal & accessory organs.*
- *Alimentary canal, or GIT: long, continuous, hollow tube that extends from the mouth to the anus.*
- *Accessory organs of digestion : salivary glands, liver, gallbladder & pancreas*

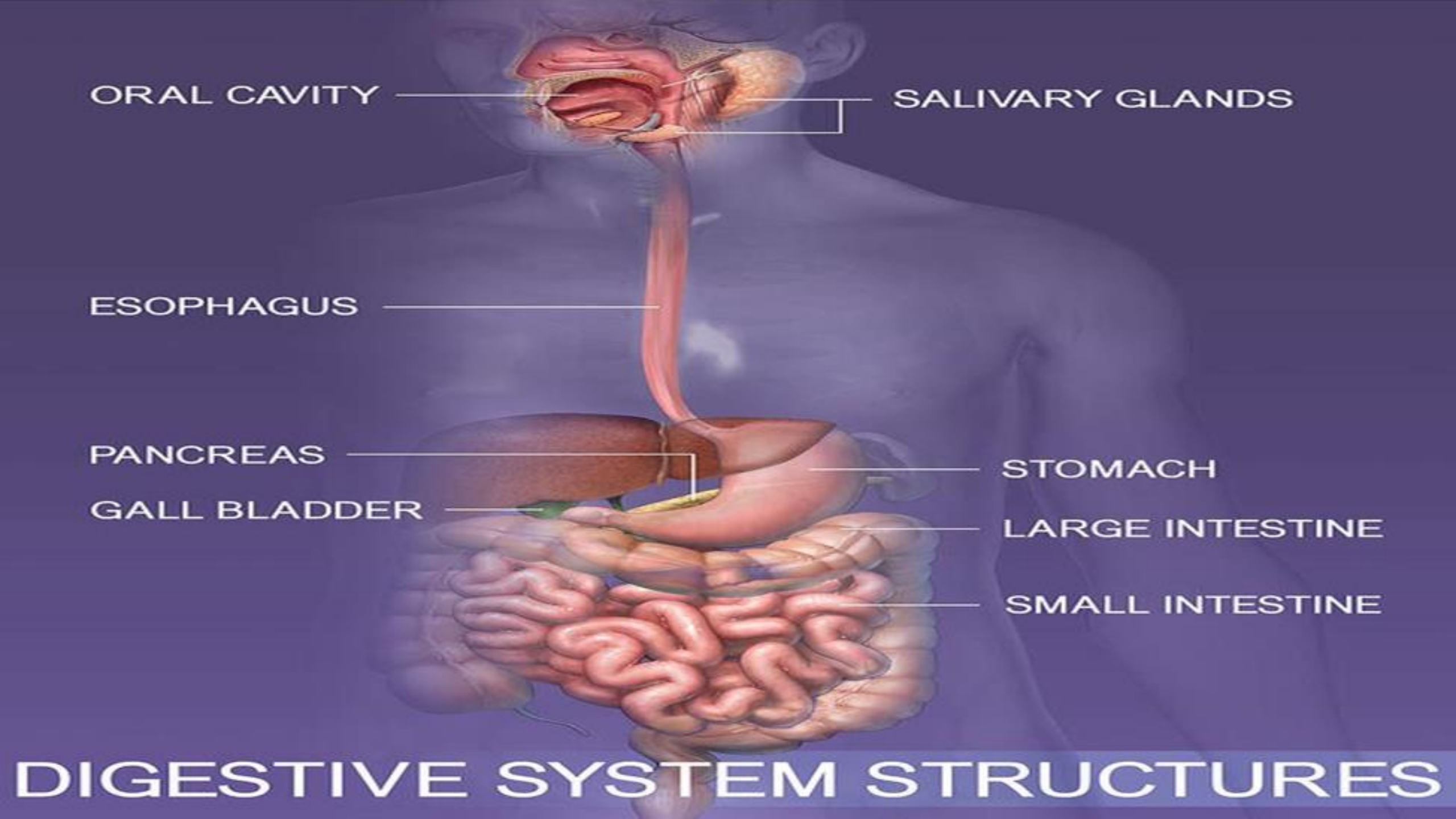
STRUCTURE OF THE GIT

Divided into two main parts:

- ***The upper tract -*** *structures that aid in ingestion & digestion of food ; mouth, esophagus, stomach & duodenum.*
- ***The lower tract*** *- consists small & large intestines.*

Small int. - absorbing almost all of the nutrients got from foods into the bloodstream

- *large int. - serves to absorb water & electrolytes & to eliminate the waste products of digestion.*


ORAL CAVITY
SALIVARY GLANDS
ESOPHAGUS
PANCREAS
GALL BLADDER
STOMACH
LARGE INTESTINE
SMALL INTESTINE
DIGESTIVE SYSTEM STRUCTURES

Pathophysiology of the GIT

Pathologies GIT are due to impairment of one or more of these simple functions (secretion, absorption, motility) & are divided into :

- *Functional types - e.g. irritable bowel syndrome (IBS), dyspepsia or*
- *Organic types - e.g. inflammatory bowel disease (IBD), colorectal cancer, peptic ulcer, gastroesophageal reflux disease (GERD), chronic gastrointestinal infection, primary bile acid diarrhea, microscopic colitis*
- *May present with nonspecific signs & symptoms*

Drugs acting on Gastrointestinal tract

- *Drugs used to treat common medical conditions involving the GIT:*
- *peptic ulcers, gastroesophageal reflux disease (GERD),Irritable bowel syndrome (IBS), emesis, diarrhea & constipation*
- ***Gastrointestinal Medications***
- *Antacids, PPI ,H2 blockers, Promotility Agents, Laxatives, Antiemetics etc*

DYSPEPSIA

Difficult digestion. Key problem due to acidity:

Symptoms *:*

- *Early satiation*
- *Bloating*
- *Heartburn*
- *Belching*
- *Nausea /vomiting*
- *Pain.*

Causative factors :

- *Gastro-oesophageal reflux disease (GORD), due to reflux of gastric contents into the oesophagus*
- *Peptic ulceration (gastric & duodenal) with erosion, damage, bleeding.*
- *Drugs : nonsteroidal anti-inflammatory drug (NSAID) use*
- *Infection : gram-negative Helicobacter pylori*

- *Imbalance between aggressive factors (gastrin, acid and helicobacter pylori) & defensive ones (bicarbonate, mucus and prostaglandins)*
- *Increased hydrochloric acid secretion*
- *Inadequate mucosal defense against gastric acid.*

***Gastritis involves inflammation*

- *Others :*
  - *Alcohol*
  - *Smoking*

Treatment approaches:

1) *Eradicating the H. pylori infection*
2) *Reducing secretion of gastric acid &*
3) *Providing agents that protect the gastric mucosa from damage*

Regulation of gastric acid secretion

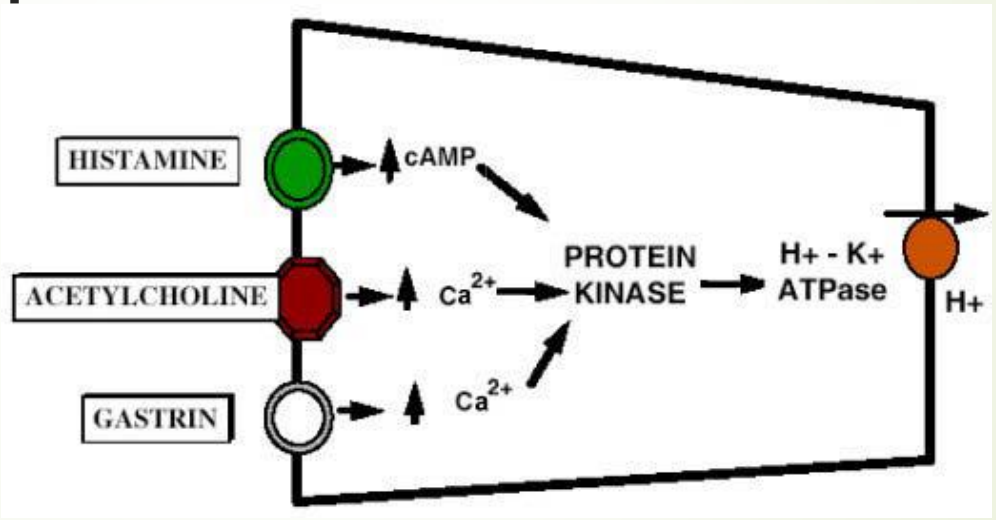
- *Gastric acid secretion originates with hydrolysis of water into hydrogen & hydroxyl ions in parietal cells.*
- *Hydrogen ions, as well as chloride ions, are actively secreted into the stomach lumen to form hydrochloric acid .*
- *Hydroxyl ions are converted to bicarbonate ions by* ***carbonic anhydrase*** *& passively enter the gastric venous blood, raising its pH.*

- *Acid is essential for activation of the **protease pepsin** to initiate protein digestion.*
- *Oxyntic cells also secrete gastric intrinsic factor, necessary for absorption of vitamin B12 & normal erythropoiesis.*
- *Damage to gastric mucosa by acid & various ingested & secreted products is prevented by **mucosal barriers**.*
- *Gastric mucosa is normally a tight epithelium, relatively impermeable to hydrogen ions.*
- *Active secretion of hydrogen ions can result in damage of mucosa.*

- *Acid secretion regulated by 3 major pathways:*
- *Neural stimulation(**Acetylcholine**) via the vagus nerve*
- *Endocrine stimulation via **gastrin** released from antral G cells,*
- *Paracrine stimulation by the local release of **histamine** from enterochromaffin-like cells.*

***In contrast, receptor binding of **prostaglandin E2** diminish gastric acid production.*

Physiological regulation of gastric acid secretion in oxyntic/parietal cells: the agonist (histamine, acetylcholine or gastrin) interacting with their own receptor leads to the activation of the H+/K+ ATPase pump, which is able to increase the hydrogen ions into the lumen



Helicobacter pylori eradication

- *Diagnosed via endoscopic biopsy of gastric mucosa or various noninvasive methods, including serology & urea breath tests.*
- *Effective therapy: long term cure ,low relapse rates*
- *Triple therapy: PPI with either metronidazole or amoxicillin plus clarithromycin, or*
- *Quadruple therapy of **bismuth subsalicylate & metronidazole** + **tetracycline** + a **PPI**, administered for 2-week course.*

H2-receptor antagonists

e.g Cimetidine, ranitidine, famotidine, nizatidine .

***MOA** -Antagonism of histamine H2 receptors(on stomach parietal cells) which are coupled via adenylyl cyclase to increase cyclic adenosine monophosphate (cAMP) which activates the proton pump→↓HCL.*

- *Highly selective.*
- *Fully reversible*
- *↓H+ concentration in gastric lumen as well as vol. of acid secretion, along with pepsin secretion from chief cells.*
- *Effective against nocturnal acid secretion (depends largely on histamine).*

Adverse effects Adverse effects: *headache, dizziness, diarrhea, and muscular pain.*

CNS effects (confusion, hallucinations) occur primarily in elderly patients or after intravenous administration, gynecomastia & galactorrhea (cimetidine)

Clinical context

- *Gastric acid secretion.*
- *Provide symptomatic relief.*

Pharmacokinetics:

- *Ranitidine t1/2(2hr): Compared to cimetidine*
- *Ranitidine is longer acting & is five- to ten-fold more potent.*
- *Ranitidine minimal side effects &* ***no antiandrogenic or prolactin-stimulating effects of cimetidine.***
- *Cimetidine inhibits cytochrome P450 & ↓metabolism of other drugs, resulting in impt drug interactions (e.g. oral anticoagulants, phenytoin, carbamazepine, tricyclic antidepressants).*
- *Ranitidine does not interact in this way.*

Inhibitors of the H+/K+-ATPase proton pump (PP1)

e.g Omeprazole , dexlansoprazole ,lansoprazole, rabeprazole , pantoprazole, esomeprazole.

***MOA** - Irreversible inhibition of the proton pump (H/K-ATPase) of gastric parietal cells.*

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PHARMACOKINETICS

- *Activated in an acidic environment which helps selectivity*
- *Superior antisecretory potency, long-lasting efficacy*
- *Acid suppression begins within 1 to 2 hours after the first dose of lansoprazole and slightly earlier with omeprazole*
- *All delayed-release formulations*
- *half-life 1.5hrs*

- *Effective orally. Taken 30 minutes before breakfast or the largest meal of the day ,for maximum effect.*
- *Metabolites of these agents are excreted in urine and feaces.*

***Pharmacokinetic characteristics have established these compounds as drugs of choice for the therapy of peptic ulcers*

Adverse effects

nausea, diarrhea, headache, GI disturbance and Bone Fractures,increased risk with long-term(1year or greater) use: hip, wrist, and spine

- *Inhibit H secretion by 90%, may lead to achlorhydria (absence of acid)*
- *Increase risk of Campylobacter infection (food poisoning) as the stomach acid sterilizes food.*

- ***CLINICAL CONTEXT***
- *PPIs ↓ the risk of bleeding from an ulcer caused by aspirin and other NSAIDs.*
- *Successfully used with antimicrobial regimens to eradicate H. pylori.*
- *Stress ulcer treatment & prophylaxis*
- *GERD, erosive esophagitis, active duodenal ulcer*
- *Zollinger-Ellison syndrome- gastrin-producing tumor causes hypersecretion of HCl).*

PROSTAGLANDINS

e.g Misoprostol

***MOA** - Postaglandin E2, produced by the gastric mucosa, inhibits secretion of HCl & stimulates secretion of mucus & bicarbonate .*

- *stable analog of prostaglandin E1.*
- *Prophylactic use considered in Pts taking NSAIDs or corticosteroids.*
- *Misoprostol produces uterine contractions, contraindicated during pregnancy.*

ADVERSE EFFECTS

- *Dose-related diarrhea & nausea , most common*

ANTIMUSCARINIC AGENTS

- *e.g. dicyclomine*
- ***MOA** - Muscarinic receptor stimulation increases GI motility & secretory activity.*
- *Used as an adjunct in the management of peptic ulcer disease.*
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ADVERSE EFFECTS

- *Cardiac arrhythmias, dry mouth, constipation, & urinary retention*

ANTACIDS

- *e.g. sodium bicarbonate, aluminium & magnesium hydroxides*

- ***MOA** - weak bases that react with gastric acid to form water & a salt, thereby ↓ gastric acidity.*
- *e.g. Calcium carbonate [CaCO3] + HCl → CO2 + CaCl2*
- *- Pepsin is inactive at a pH greater than 4, antacids also reduce pepsin activity.*

- *Antacids more quickly & efficiently neutralize stomach acid*
- *Action only temporary*
- *Food delays stomach emptying allowing more time for the antacid to react..*

- ***CLINICAL CONTEXT***
- *Aluminum- and magnesium-containing antacids are used for symptomatic relief of peptic ulcer disease and GERD*
- *Promote healing of duodenal ulcers.*
- ***ADVERSE EFFECTS***
- *Aluminum hydroxide (constipation) and magnesium hydroxide (diarrhea).*

***Preparations that combine these agents aid in normalizing bowel function.*

ALGINATES

- *Alginates may be combined with antacids (e.g. Gaviscon).*
- *The alginic acid, when combined with saliva, forms a viscous foam which floats on the gastric contents, forming a raft which protects the oesophagus during reflux.*

MUCOSAL PROTECTIVE AGENTS

Cytoprotective compounds e.g. Sucralfate, Bismuth subsalicylate

- ***MOA -*** *have several actions that enhance mucosal protection mechanisms, thereby preventing mucosal injury, reducing inflammation & healing existing ulcers.*

Sucralfate*: Complex of aluminum hydroxide and sulfated sucrose. Form complex gels with epithelial cells, creating a physical barrier that impairs diffusion of HCl*

- *Prevents degradation of mucus by pepsin and acid.*
- *Effective for the treatment of duodenal ulcers and prevention of stress ulcers*
- *use is limited due to the need for multiple daily dosing*

- ***Bismuth subsalicylate***: *Antimicrobial actions, inhibits activity of pepsin, increases secretion of mucus, & interacts with glycoproteins in necrotic mucosal tissue to coat & protect the ulcer.*

PROKINETIC DRUGS

e.g. Domperidone, metoclopramide

MOA - Cause gastric emptying.

- *Movement of gastric contents from stomach to duodenum – of benefit in GERD.*
- *Domperidone (dopamine receptor antagonist): increased closure of oesophageal sphincter (good for reflux disease) and opens lower sphincter.*
- *Metoclopramide (dopamine receptor antagonist): acts locally to increase gastric motility and emptying*

THE ULCEROGENIC EFFECTS OF NSAIDS (and oral steroids)

Oral NSAIDS (commonly) and corticosteroids (less commonly) associated with peptic damage/ulceration.

- *NSAIDs inhibit cyclooxygenases*
- *COX exists as two isoforms:*
- *COX-1: physiological, e.g. gastric protection*
- *COX-2: pathological, involved in inflammation.*

- *Most NSAIDs inhibit both and cause gastric damage.*
- *COX-2-selective inhibitors (celecoxib) were developed to have fewer gastrointestinal side-effects.*
- *To minimise gastrointestinal damage use a PPI for prophylaxis.*
- *Give NSAID in combination with misoprostol, a stable prostaglandin E1 analogue, which acts on prostanoid receptors to inhibit gastric H secretion*

PHARMACOTHERAY OF EME
VERTIGO,DIARRHOEA, IBS &

- *Nonspecific symptoms*
- *Nausea, vomiting, constipation, & diarrhea ,*

common adverse effects of oral medications.

- *Symptoms often resolve , when severe or prolo*

may lead to serious consequences unless drug therapy is initiated.

EMESIS (VOMITING)

- *Nausea & vomiting may occur in a variety of conditions e.g.motion sickness, pregnancy, or hepatitis, drugs(chemotherapy)*

Mechanisms of vomiting

The whole mechanism is guided & controlled by the brain & its vomiting centre.

2 brainstem sites have key roles in the vomiting reflex pathway.

1. *Chemoreceptor trigger zone (CTZ)- located in the outside of blood-brain barrier.*

- *CTZ contains receptors for dopamine, serotonin, opioids, acetylcholine & neurotransmitter substance P.*
- *When stimulated, each of these receptors gives rise to pathways leading to nausea & vomiting.*

2. Vomiting center - located in the lateral reticular formation of the medulla, coordinates the motor mechanisms of vomiting.

***The vestibular system functions mainly in motion sickness*

- ***Emetic actions of chemotherapeutic agents***
- *Agents e.g chemotherapeutic agents can directly activate the medullary chemoreceptor trigger zone or vomiting center*
  - *Neuroreceptors play roles in vomiting*
    - *Dopamine receptor Type 2*
    - *Serotonin Type 3 (5-HT3) from cell damage(GIT and pharynx)*
  - *Drugs from at least 8 different classes are used to prevent nausea & vomiting*

ANTIHISTAMINES & ANTICHOLINERGICS

- *Effective for treating simple nausea e.g. nausea due to motion sickness*

Scopolamine – *Common antichlinergic drug used for motion sickness*

- *Antihistamines- cinnarizine & meclizine, also effective but may cause significant drowsiness in some pts.*

***Drugs used to treat motion sickness are most effective when taken 20 to 60 minutes before travel is expected.*

Other antihistamines - Promethazine

Phenothiazine & Phenothiazine-like Drugs

MOA *-act by blocking dopamine receptors*

- *Effective against low or moderately emetogenic chemotherapeutic agents.*
- *Adverse reactions - extrapyramidal symptoms & sedation*
- *Serious nausea & vomiting associated with antineoplastic therapy is sometimes treated with the phenothiazines.*

- *To prevent loss of the antiemetic medication due to vomiting, some of these medications are available through the intramuscular (IM), IV, and/or suppository routes.*
- *Nonphenothiazine antipsychotics that have high antiemetic activity include* ***haloperidol*** *and* ***droperidol*****.**

Serotonin (5-HT3) Antagonists

e.g. dolasetron , granisetron , ondansetron, palonosetron

MOA-Specific antagonists of the 5- HT3 receptor .Selectively block 5-HT3 receptors in the periphery & brain

- *Preferred drugs for the pharmacotherapy of serious nausea & vomiting caused by antineoplastic therapy, radiation therapy, or surgical procedures.*
- *usually given prophylactically, just prior to antineoplastic therapy. Intravenous (IV), oral & transdermal patch forms are available.*

ADVERSE EFFECTS: *headache, constipation or diarrhea & dizziness*

DOPAMINE RECEPTOR ANTAGONISTS

- *e.g. Metoclopramide , Domperidone*
- *MOA - Act by blocking dopamine D2 receptors in the CTZ & peripherally*

Antidopaminergic side effects: *sedation, diarrhea & extrapyramidal symptoms, limit its high-dose use.*

BENZODIAZEPINES

- *lorazepam & alprazolam anti emetic property low*
- *Their beneficial effects may be due to their sedative, anxiolytic & amnesic properties.*

CORTICOSTEROIDS

- *e.g. Dexamethasone, methylprednisolone*
- *Their antiemetic mechanism is not known, but it may involve blockade of prostaglandins.*
- *Effective against mildly to moderately emetogenic chemotherapy & postsurgical nausea & vomiting.*
- *Reserved for the short-term therapy of acute cases because of the potential for serious long-term adverse effects*

Class of medication	Common uses	Common side effects
Anticholinergic Scopolamine	Possible adjunct for cytotoxic chemotherapy, prophylaxis and treatment of motion sickness	Drowsiness, dry mouth, vision disturbances
Antihistamines Cyclizine Dimenhydrinate Diphenhydramine Meclizine	Migraine, motion sickness, vertigo	Drowsiness
Dopamine antagonist Chlorpromazine Metoclopramide Prochlorperazine Promethazine	Migraine, motion sickness, post-chemotherapy nausea and vomiting, postoperative nausea and vomiting, severe episodes of nausea and vomiting, vertigo	Extrapyramidal symptoms (e.g. dystonia, tardive dyskinesia), orthostatic hypotension, sedation
Serotonin antagonist Dolasetron Ondansetron Granisetron	Post-chemotherapy nausea and vomiting, severe nausea and vomiting, acute gastroenteritis	Asthenia, constipation, dizziness, mild headache

EMETICS

- *On some occasions, it is desirable to stimulate the vomiting reflex with drugs called emetics.*
- *Indications for emetics include ingestion of poisons & overdoses of oral drugs.*
- ***Ipecac syrup**, given orally, or **apomorphine**, given subcutaneously, will induce vomiting in about 15 minutes.*

ANTIDIARRHEAL DRUGS

- *↑ motility of the GIT & ↓ absorption of fluid .*
- *Acute diarrhoea is usually due to either a drugs, bacterial or viral infection*
- *Antidiarrheal drugs include antimotility agents, adsorbents & drugs that modify fluid and electrolyte transport.*

ORAL REHYDRATION (ORT)

- *ORS – mixture of electrolytes and carbohydrates dissolves in water*
- *Most effective treatment*

.

MOA- Uses the sodium- glucose cotransport mechanism to passively absorb water across the intestinal mucosa, leading to rehydration .

ANTIMOTILITY AGENTS

- *e.g. diphenoxylate, loperamide, codeine*
- *Analogs of Pethidine (meperidine) & opioid-like actions on the gut*

MOA - Activate presynaptic opioid receptors in the enteric nervous system to inhibit acetylcholine release & ↓ peristalsis .

ADVERSE EFFECTS

Drowsiness, abdominal cramps, dizziness.

Antimuscarinic agents *e.g. dicycloverine*

MOA - *block muscarininc receptors on the smooth muscle, leading to ↓ GI motility.*

Tricyclic antidepressants *(TCAs) are also constipating as a side-effect through antagonism of muscarinic receptors.*

ADSORBENTS

- *e.g. Methylcellulose , aluminum hydroxide, kaolin, pectin,*
- ***MOA** - act by adsorbing intestinal toxins or microorganisms &/or by coating or protecting the intestinal mucosa.*
- *- Kaolin & pectin ↑ viscosity of the gut contents & adsorb bacteria & toxins.*
- *Much less effective than antimotility agents*
- *Can interfere with the absorption of other drugs*

AGENTS THAT MODIFY FLUID AND ELECTROLYTE TRANSPORT

- *e.g. Bismuth subsalicylate*
- *decreases fluid secretion in the bowel.*
- *Its action may be due to its salicylate component as well as its coating action.*
- *used for traveler's diarrhea*

ADVERSE EFFECTS

- *black tongue & black stools.*

LAXATIVES

- *Commonly used to accelerate the movement of food through the gastrointestinal tract.*
- *Classified on the basis of their mechanism of action*
- *Cause electrolyte imbalances when used chronically.*
- *Risk of dependency for the user.*
- *Stimulants laxatives ,Bulk laxatives ,Saline and Osmotic laxatives ,Stool softeners (emollient laxatives or surfactants), Lubricant laxatives ,Chloride channel activators*

CONSTIPATION

- *Constipation is altered bowel habits with fewer than three motions a week.*

Cause

- *Diet - lacking in roughage (often be manage*

balanced diet)

- *Drug-induced:*
  - *opioids*
  - *TCAs*
  - *antimuscarinic drugs*
  - *diuretics (due to dehydration).*

A. Stimulant laxatives- *Simulate peristalsis potentially by altering GI water & electrolyte secretion → net intestinal fluid accumulation & laxation.*

Senna

- *Is active ingredient is a group of sennosides, a natural complex of anthraquinone glycosides.*
- *Taken orally, it causes evacuation of the bowels within 8 to 10 hours.*
- *It also causes water and electrolyte secretion into the bowel .*

Bisacodyl

- *Potent stimulant of the colon.*
- *It acts directly on nerve fibers in the mucosa of the colon.*

Castor oil

- *Broken down in the small intestine to **ricinoleic acid**, which is very irritating to the stomach and promptly increases peristalsis.*

***Pregnant patients should avoid castor oil because it may stimulate uterine contractions.*

- ***B. Bulk laxatives***
- *The bulk laxatives include* ***hydrophilic colloids*** *(from indigestible parts of fruits and vegetables).*
- ***MOA****- They form gels in the large intestine, causing water retention & intestinal distension, thereby increasing peristaltic activity.*
- *Similar actions are produced by* ***methylcellulose, psyllium seeds, and bran*** *for chronic constipation.*

C. Saline and Osmotic laxatives

e.g. Magnesium citrate , sodium phosphate,magnesium hydroxide, Lactulose

- ***MOA*** *- nonabsorbable salts (anions and cations) that hold water in the intestine by osmosis* and distend the bowel, increasing intestinal activity and producing defecation in a few hours.
- **Lactulose -** semisynthetic disaccharide sugar that also acts as an osmotic laxative.

- *Lactulose cannot be hydrolyzed by intestinal enzymes.*
- *Oral doses degraded in colon by colonic bacteria into lactic, formic & acetic acids which ↑osmotic pressure→ fluid accumulation, colon distension, soft stools & defecation.*
- *Lactulose used for the treatment of hepatic encephalopathy, due to its ability to reduce ammonia levels.*

Polyethylene glycol*(PEG) Electrolyte solutions used as colonic lavage solutions to prepare the gut for radiologic or endoscopic procedures.*

- ***D. Stool softeners (emollient laxatives or surfactants)***
- *Surface-active agents that become emulsified with the stool produce softer feces and ease passage.*
- *e.g. docusate sodium, docusate calcium,docusate potassium.*
- ***Take days to become effective,often used for prophylaxis rather than acute treatment.*

- ***E. Lubricant laxatives e.g.*** *Mineral oil, glycerin*
- *suppositories considered to be lubricants.*
- *They facilitate the passage of hard stools.*
- ***F. Chloride channel activators*** *e.g Lubiprostone*
- ***MOA*** *- work by activating chloride channels to increase fluid secretion in the intestinal lumen.*
- *Eases the passage of stools & causes little change in electrolyte balances.*
- *Nausea is a relatively common side effect with lubiprostone.*

LAXATIVES

Type	Laxative agent	Mechanism of action	Possible side effects
Bulking forming laxatives	Natural fibres (e.g., psyllium)	Intraluminal H_2o binding, bulk forming and decrease stool consistency	Bloating, flatulence
	Semi-synthetic fibres (es. methylcellulose)		
	synthetic fibres (e.g., Polyethylene glycol polycarbophil: Macrogol)		
Osmotic laxatives	Magnesium hydroxide, magnesium citrate, magnesium sulfate, sodium phosphate.	Interstitial H_2o binding	hydroelectrolytic alterations
Disaccharides and alditols	Lactulose, sorbitol.	Interstitial H_2o binding	Bacterial fermentation with bloating and flatulence (low efficacy in *slow transit constipation*)
Emollients laxatives	Paraffin oil, docusate sodium	Intraluminal H_2o binding, bulk forming and decrease stool consistency	*Discomfort*, abdominal pain, cramping
Stimulant laxatives	diphenylmethane derivatives (bisacodyl, sodium picosulfate)	Stimulating action on enteric nerves with decrease in peristaltic contractions.	*Discomfort*, abdominal pain, cramping
	Anthraquinones (senna, aloe, cascara)	Decrease in colic absorption of H_2o and electrolytes	

IRRITABLE-BOWEL SYNDROME

- *common, long-standing disorder & may involve pain and bloating, relieved by defecation.*
- *There may be episodes of diarrhoea and/or constipation.*

Treatment may involve:

- *lactulose or loperamide for symptoms*

- *Antispasmodic agents e.g. antimuscarinics, which inhibit parasympathetic activity, or*

Mebeverine, direct relaxant of GI smooth muscle

- *Amitriptyline (TCA) - has antimuscarinic effects, may alter the sensitivity of sensory nerves .*
- *widely used in low doses ,provides pain relief.*

INFLAMMATORY BOWEL DISEASE

- *Crohn's disease and ulcerative colitis*
- *Characterised by chronic inflammation with pain and bloody diarrhoea.*
- *Managed via anti-inflammatories and immunosuppressants.*

5-Aminosalicylates *e.g. sulphasalazine, mesalazine*

- *These agents release 5-aminosalicylate (5-ASA).*
- *5-ASA inhibits leukotriene and prostanoid formation, scavenges free radicals and decreases neutrophil chemotaxis.*

Corticosteroids *e.g. Budesonide*

- *Anti-inflammatory, immunosuppressive actions.*

Immunosuppressants

- *Azathioprine, ciclosporin, methotrexate are used.*