PHARMACOLOGY

THE INNERVATION AND HORMONES OF THE GIT

➢NEURONAL CONTROL

GIT activity is controlled by the enteric nervous system –part of the autonomic nervous system-
There are two principal intramural plexuses in the tract:
1. The myenteric plexus (Auerbach's plexus)
2. The submucous plexus (Meissner's plexus)

- These plexuses are inter connected and their ganglion cells receive preganglionic parasympathetic fibers from the vagus nerve.
- Some sympathetic fibers terminate in these plexuses, where they inhibit Ach secretion .
- The neurons within the plexuses constitute the enteric nervous system and secrete Ach, NE, serotonin, purines, nitric oxide and pharmacologically active peptides.
- The enteric plexus also contains sensory neurons, which respond to mechanical and chemical stimuli.

➢HORMONAL CONTROL

- The endocrine secretions are mainly peptides synthesised by endocrine cells in the mucosa (gastrin and cholecystokinin)
- The paracrine secretions include many regulatory peptides released from special cells in the GIT.
- In the stomach the most important of these is histamine.

GASTRIC SECRETION

- The stomach secretes 2.5 liters of gastric juice daily.
- The principal exocrine components are prorennin and pepsinogen secreted by the chief cells, HCl and intrinsic factor secreted by the parietal cells.
- HCl is important for promoting proteolytic digestion of foodstuffs, iron absorption and killing pathogens.
- Mucus-secreting cells also exist in large numbers in the gastric mucosa.
- Bicarbonate ions are secreted and trapped in the mucus, creating a gel-like protective barrier that maintains the mucosal surface at a pH of 6–7 in the face of a much more acidic environment (pH 1–2) in the lumen.(protects the stomach from corrosive effects HCl & pepsin)
- Alcohol and bile can disrupt this protective layer.
- Locally produced 'cytoprotective' prostaglandins stimulate the secretion of both mucus and bicarbonate.
- Disturbances in these secretory and protective mechanisms are involved in the pathogenesis of peptic ulcer, gastro-oesophageal reflux disease (GORD) and injury caused by non- steroidal anti-inflammatory drugs (NSAIDs).

PHARMACOLOGY

Physiology of gastric Secretion:

➢Parietal cells secrete 2 liters of acid/ day.
➢Optimal pH (between 1.8-3.5) for the function of the digestive enzyme pepsin.
➢Stimulation of acid secretion involves translocation of H+/K+-ATPase to the apical membrane of parietal cell.
➢H+/K+-ATPase (proton pump) uses the energy derived from ATP hydrolysis to pump H+ into the lumen in exchange for potassium ions.
➢*** Chloride and hydrogen ions are secreted separately from the cytoplasm of parietal cells and mixed in the canaliculi.

Stimulants of acid secretion:

1-Ach from enteric neurons.
2-Histamine from ECL (enterochromaffin - like) cells.
3-Gastrin released by G cells.
➢ Somatostatin in D cells inhibits acid secretion.
➢ Gastric pH < 3 --> gastric D cells release somatostatin It inhibits acid secretion by:
1- direct effects on parietal cells.
2- inhibiting release of histamine & gastrin.

Three phases in gastric acid secretion.

1-Cephalic Phase: sight, smell, taste or thought of food, activate enteric neurons via vagus
In humans, the major effect of gastrin is indirect through the release of histamine from ECL cells not through direct parietal cell stimulation.
2-Gastric Phase: Food stretch stomach walls activating a neural reflex to stimulate acid secretion.
Peptides & amino acids stimulate G cells to release gastrin.
Food acts as a buffer, raising the pH & thus removing the stimulus for somatostatin secretion.
3-Intestinal Phase: Once chyme enters the duodenum, it activates negative feedback mechanisms to reduce acid secretion.

The principal clinical indications for reducing acid secretion are:

1- peptic ulcer (both duodenal and gastric).
2-GORD (gastroesophageal reflux disease) (gastric secretion causes damage to the oesophagus). If untreated, GORD can cause dysplasia of the esophageal epithelium which may progress to apotentially dangerous pre-cancerous condition called Barrett's esophagus.
3-Zollinger–Ellison syndrome (a rare hypersecretory condition caused by a gastrin-producing tumour).
➢ The reasons why peptic ulcers develop are not fully understood, although infection of the stomach mucosa with Helicobacter pylori causes chronic gastritis , now considered to be a major cause of ulcers (especially of duodenal ulcer).
➢ Many NSAIDs cause gastric bleeding and erosions by inhibiting cyclo-oxygenase-1, the enzyme responsible for synthesis of protective prostaglandins.
➢ Therapy of peptic ulcer and reflux oesophagitis aims to decrease the secretion of gastric acid with H2 receptor antagonists or proton pump inhibitors, and/or to neutralise secreted acid with antacids / These treatments are often coupled with measures to eradicate H. pylori

Peptic ulcer : A defect in the lining of the stomach or the duodenum.

➢ **Causes**
1-Helicobacter pylori (most common).
2-Drugs such as aspirin & other NSAIDs
3-Other factors: Smoking, Stress, alcohol. Gastrinomas such as ZollingerEllison syndrome
➢ **Symptoms**:
1-burning pain in stomach between meals or at night, bloating, heartburn, nausea or vomiting.
In severe cases, symptoms include:
1-Dark or black stool (due to bleeding)
2-Vomiting blood (hematemesis)
3-Weight loss & severe painin the mid to upper abdomen.

➢ **Complications of peptic ulcer:**
1-Gastrointestinal bleeding.(Sudden large bleeding can be life threatening).
2-Cancer (Helicobacter pylori as the etiological factor)
3-Perforation (hole in the wall) Penetration.

➢ **Treatment options:**
Reduce acid secretion or Neutralize acid in the lumen
Protect the mucosa from acid destruction
Antibiotics to eradicate Helicobacter pylori. If this is successful then the ulcer should begin to heal on its own.

Neutralization of acid (Antacids)

- **Nonprescription** remedies for treatment of **heartburn** & **dyspepsia**.
- Given 1 hour after a meal effectively neutralizes gastric acid for up to 2 hours.

<table>
<tr><th>Aluminum</th><th>Magnesium</th><th>Magnesium trisilicate</th><th>Calcium carbonate</th><th>Sodium bicarbonate</th></tr>
<tr><td>antacids cause constipation ,
interfere with
absorption of many drugs.

AL(OH)3 + HCl -----> ALCl3 + H2O</td><td>antacids have laxative action; diarrhea.
ionic magnesium stimulates gastric release (acid rebound)

2HCl + Mg(OH)2 ----> MgCl2 + 2H2O

to memorize it quickly
Doctor of Medicine “MD”
MD M = Magnesium
D = Diarrhea</td><td rowspan="2">slow-acting antacid

(longer duration of action)</td><td rowspan="2">associated with “acid rebound”

with excessive chronic use,
it may cause :
milk-alkali syndrome with elevation of serum calcium, phosphate , urea, nitrogen, creatinin & bicarbonate levels

2HCl + CaCO3 ---> CaCl2 + CO2 + H2O</td><td rowspan="2">1. Should be avoided as it aggravate CHF & counteracts diuretic therapy for hypertension

2. Short duration of action, followed by acid rebound

3. Highly absorbed, potentially causing metabolic alkalosis

4. CO2 results in gastric distention and belching

NaHCO3 + HCl → NaCl + H2O + CO2</td></tr>
<tr><td colspan="2">Combination of Magnesium & aluminum antacids are most commonly used
(No diarrhea or constipation).</td></tr>
</table>

H2-Receptor Antagonists

	Cimetidine	Ranitidine	Famotidine	Nizatidine
Absorption	Rapidly absorbed from intestine.			
Metabolism	50 % first-pass metabolism bioavailability			little first-pass metabolism
Duration of action	6–10 hours, given **twice** daily.			
Mechanism of action	-Inhibit 90% of nocturnal acid (depends on histamine). -Modest impact on meal-stimulated acid secretion (which is stimulated by gastrin, Ach and histamine). -Inhibit 60% of day-time, meal stimulated acid. -Inhibit 60-70% of total 24-h acid secretion.			
Clinical Uses	1. Gastroesophageal Reflux Disease (GERD) -hence PPI are preferred -Taken prophylactically before meals. -In erosive esophagitis H2 antagonists healing is less than 50% 2. Non Ulcer Dyspepsia -Over-the-counter agents for treatment of intermittent dyspepsia not caused by peptic ulcer. 3. Prevention of Bleeding from Stress-Related Gastritis -IV H2 antagonists are preferable over IV PPI because of their proven efficacy and lower cost. 4. Peptic Ulcer Disease: - Replaced by PPI. - Healing rate more than 80-90% after 6-8 wks. - Not effective in the presence of **H. pylori**. - Not effective if NSAID is continued			
Adverse Effects	may cause gynecomastia & impotence in men (antiandrogenic effects) and galactorrhea in women	-Extremely safe drugs -Diarrhea, headache, fatigue, myalgias, and constipation (3%).		
Drug Interactions	**inhibits cytochrome P450** enzymes so can **increase** half life of many drugs	binds 4-10 times less	binding is negligible	

Proton Pump Inhibitors (PPIs)

➢ **Among the most widely prescribed drugs worldwide due to their outstanding efficacy and safety.**

	Omeprazole (oral)	**Lanzoprazole (oral and IV)**	**Esomeprazole (oral and IV)**	**Rabeprazole (oral)**	**Pantoprazole (oral and IV)**	**Immediate-Release Omeprazole**
Notes	available as capsules of enteric-coated granules, why? Because all PPIs are destroyed by the acidity of the stomach, they are coated to bypass the stomach to be released in the intestine. So, their absorption takes some time.			are tablets with a pH-sensitive coating. (Dissolves only in alkaline medium in the intestine.)		contains sodium bicarbonate to protect the drug from acid degradation results in rapid response
	Prodrugs, released in the intestine (Destroyed by acid).					
	1-Lipophilic weak bases, absorbed in small intestine and delivered to parietal cell through the blood. 2-Drug is protonated and "trapped" in acidic canaliculi. 3-Concentrated more than 1000-fold in the parietal cells. 4-Converted to the active form which covalently binds the H+/K+ ATPase enzyme and inactivates it. 5-Have short half lives but effect lasts for 24 hours,Why >> no. 6 6-because At least 18 hours are required for synthesis of new pump molecules. 7-Inhibit both fasting & meal-stimulated secretion (90-98% of 24-hour secretion). 8-The full acid-inhibiting potential is reached in 3 to 4 days.					
Clinical Uses	1. Gastroesophageal Reflux (GERD): -The most effective agents in all forms of GERD 2. Nonulcer Dyspepsia: -Modest activity.10-20% more beneficial than a placebo 3. Stress- Related Gastritis: -Oral immediate- release omeprazole administered by nasogastric tube -For patients without a nasoenteric tube, IV H2- blockers are preferred because of their proven efficacy. 4. Gastric acid hypersecretory states, including Zollinger -Ellison syndrome: -Usually high doses of omeprazole are used. 5. Peptic Ulcer Disease: -They heal more than 90% of cases within 4-6 weeks. -H. Pylori - associated ulcers: PPI eradicate H. pylori by direct antimicrobial activity and by lowering MIC(minimum inhibitory concentration) of the antibiotics. Triple Therapy: PPI twice daily + Clarithromycin 500 mg twice daily +Amoxicillin 1gm twice daily ,OR, Metronidazole 500mg twice daily -NSAID-associated ulcers: Healing despite continued NSAID use Also used to prevent ulcer of NSAIDs -Rebleeding peptic ulcer: Oral or IV. High pH may enhance coagulation and platelet aggregation.					
Adverse Effects	1-Well tolerated. 3-Reduction of cyanocobalamine absorption. 5-Increased serum gastrin levels causes: 1. Chronic inflammation in gastric body. 2. Atrophic gastritis and intestinal metaplasia.			2 -May cause headache, diarrhea, abdominal pain, nausea & dizziness 4 -Increased risk of GI and pulmonary infection.		
Drug Interactions	May affect absorption of drugs due to decreased gastric acidity like **digoxin** and **ketoconazole**					

Mucosal Protective Agents

1-Both mucus and epithelial cell-cell tight junctions restrict back diffusion of acid and pepsin.
2-Epithelial bicarbonate secretion.
3-Blood flow carries bicarbonate.
4-injured epithelium are repaired by **restitution**.
5-Mucosal prostaglandins stimulates mucus and bicarbonate secretion and mucosal blood flow.

	Sucralfate	Prostaglandin Analogs	Colloidal Bismuth Compounds:	
		Misoprostol	Bismuth subsalicylate	Bismuth subcitrate
Notes	1-A salt of sucrose complexed to sulfated aluminum hydroxide 2-In the stomach, It breaks down into sucrose sulfate (strongly negatively charged) and an aluminum salt. 3-The negatively charged sucrose sulfate binds to positively charged proteins in the base of ulcers or erosion, forming a physical barrier that restricts further caustic damage and stimulates mucosal prostaglandin and bicarbonate secretion. 4-Acts for 6 hours. 5-Less than 3% of intact drug and alumnum is absorbed.	• A methyl analog of **PGE1**. • Half-life is less than 30 min • Administered 3-4 times daily. 1. Stimulates mucus & bicarbonate secretion. 2. Enhances mucosal blood flow. 3. Acts on parietal cells, reducing histamine- stimulated cAMP production and causing modest acid inhibition. 4. Stimulates intestinal electrolyte & fluid secretion. 5. Increase intestinal motility 6. Uterine contractions	➢ Bismuth is minimally absorbed from GIT (< 1%). ➢ A mucosal protective agent, provides coat on the ulcer. ➢ Reduce the gastric HCL secretion. ➢ Reduce pepsin secretion. ➢ Stimulates the PGE secretion. ➢ Decrease H+ ion back diffusion. ➢ Help in eradication of H. pylori (anti microbial effect).	
			reduces stool frequency and liquidity in acute infectious diarrhea, due to salicylate inhibition of intestinal prostaglandin and chloride secretion.	–
Clinical Uses	- 1 g four times daily on an empty stomach (through a nasogastric tube) reduces the incidence of upper GI bleeding in critically ill patients hosptalized in the intensive care unit. - Prevention of stress-related bleeding because acid inhibitory therapies may increase the risk of nosocomial pneumonia (an infection of the lungs that occurs during a hospital stay)	**Prevention of NSAID-induced ulcers** in high-risk patients. Not widely used for this purpose because of: 1. side effects. 2. need for multiple daily dosing. 3. PPI may be as effective and better tolerated. 4. Cyclooxygenase2-selective NSAIDs are an option for such patients.	• Has direct antimicrobial effects & binds enterotoxins, so useful in preventing & treating **traveler's diarrhea**. • Widely used for the **nonspecific** treatment of **dyspepsia** and **acute diarrhea**. • Has direct antimicrobial activity against H pylori and used as second-line therapy for the eradication of H pylori infection (PPI with bismuth subsalicylate , tetracycline and metronidazole for 10–14 days).	–
Adverse Effects	• Not absorbed, so no systemic adverse effects. • Constipation (2%) due to the aluminum salt. • **Caution** in renal insufficiency . (Aluminum may be little absorbed causing renal insufficiency).	Diarrhea and cramping abdominal pain (10–20%). **it should not be used during pregnancy**	• Blackening of the stool and the tongue. • Prolonged usage may rarely lead to bismuth toxicity, resulting in **encephalopathy**.	
Drug Interactions	Sucralfate may bind to other medications, impairing their absorption.	No significant drug interactions.	–	

Drugs Stimulating GI Motility

	Prokinetic agents	Cholinomimetic Agents		Dopamine D2-receptor antagonists	
		Bethanechol	**Neostigmine**	**Metoclopramide**	**Domperidone**
Notes	1- Gut distention (increased intraluminal pressure) stimulates 5-HT release from EC (enterochromaffin) cells. 2- Serotonin causes stimulation of 5-HT3 receptors on the extrinsic afferent nerves which are parts of the vagus nerve, this stimulation causes nausea, vomiting, or abdominal pain. 3- 5-HT also stimulates 5-HT1P receptors of the intrinsic primary afferent nerves (IPANs) which activate the enteric neurons responsible for peristaltic and secretory reflex activity. 4-Stimulation of 5-HT4 receptors (5-HT4R) on presynaptic terminals of IPANs enhances release of ACh & calcitonin gene related peptide (CGRP), promoting reflex activity So a quick recap of the receptors; Gut distension → 5-HT release causes: 1- 5-HT3 stimulation (Afferent Vegas nerve) → nausea, vomiting, abdominal pain 2- 5-HT1P stimulation (IPANS) → peristaltic and secretory reflux activity. 3- 5-HT4 stimulation (presynaptic IPANS) → enhance Ach & calcitonin → more reflux activity	Stimulates muscarinic **M3** receptors on muscle cells and at myenteric plexus synapses.	**AchE inhibitor** enhances gastric, small intestine, and colonic emptying.	These agents block D2 receptors causing: -increase esophageal peristaltic amplitude. -increase lower esophageal sphincter pressure. -enhance gastric emptying. -have no effect on small intestine or colonic motility. ***Also block dopamine D2 receptors in the chemoreceptor trigger zone of the medulla (area postrema), resulting in potent **anti nausea and antiemetic actions.**	
Clinical uses	1-Increasing lower esophageal sphincter pressures, useful for GERD 2-Improving gastric emptying, helpful for gastroparesis and postsurgical gastric emptying delay 3-Stimulation of the small intestine useful for postoperative ileus 4-Enhancing colonic transit, useful in the treatment of constipation	Was used for the treatment of GERD and gastroparesis.	1- IV neostigmine used for the treatment of acute large bowel distention (acute colonic pseudo-obstruction) 2- Administration of 2 mg results in prompt colonic evacuation of flatus and feces	1- Gastroesophageal Reflux Disease • Not effective with erosive esophagitis, so in this condition, we use drugs like proton pump inhibitors. • Not superior to antisecretory agents. • Used mainly in combination with antisecretory agents (such as PPI and H2 blockers) in patients with refractory heartburn. 2- Impaired Gastric Emptying (Gastroparesis) • Widely used in post surgical and diabetic gastroparesis 3-Nonulcer Dyspepsia 4-Prevention of Vomiting 5-Postpartum Lactation Stimulation. **Domperidone** is used to promote postpartum lactation.	
Adverse Effects	–	no longer used, because of the severe side effects and development of better drugs.	Cholinergic effects include excessive salivation, nausea, vomiting, diarrhea, and bradycardia.	crosses BBB so can cause: Restlessness, drowsiness, insomnia, anxiety, agitation, extrapyramidal symptoms (dystonia, akathisia,parkinsonian features) and tardive dyskinesia.	does not cross the BBB, so does not cause CNS effects ***medulla (area posterma) is out of the BBB
				Both drugs can elevate serum prolactin levels causing galactorrhea, gynecomastia, impotence and menstrual disorders	

The enteric nervous system can independently regulate GI motility and secretion.
The myenteric interneurons control:
peristaltic reflex and promoting release of excitatory mediators proximally and inhibitory mediators distally

Motilin may stimulate excitatory neurons or muscle cells directly.
Dopamine acts as an inhibitory neurotransmitter in the GIT, decreasing the intensity of esophageal and gastric contractions.

Laxatives

Intermittent constipation is best prevented with:

- A high-fiber diet.
- Adequate fluid intake.
- Responding to nature's call.
- Regular exercise.

Bulk-Forming Laxatives	Stool Surfactant Agents (Softeners)	Lubricant/Emollient
1-Indigestible, hydrophilic colloids that absorb water, forming a bulky, emollient gel that distends the colon and promotes peristalsis 2-Effective within 1-3 days. 3-Common preparations include natural plant products (psyllium, methylcellulose, bran) and synthetic fibers (polycarbophil). 4-Bacterial digestion of plant fibers within the colon may lead to increased **bloating and flatus.**	**1.Docusate** ➢ Detergents or surfactants that act as stool-wetting and sto-olsoftening agents, allowing the mixing of water, lipids, and fecal matter. ➢ Alters intestinal permeability and increases net water and electrolyte secretions in the intestine. ➢ **Orally**: Softening of feces within 1-3 days ➢ **Rectally**: effective within 5 to 20 minutes. ➢ Used in symptomatic treatment of constipation & in painful anorectal conditions such as hemorrhoids and anal fissures. **2. Glycerin suppository.** ➢ works by irritating the lining of the intestine and increasing the amount of fluid, making it easier for stools to pass	1-Site of Action: **Colon**. 2-Onset of Action: 6 - 8 hours. 3-Causing lubrication of the stool & make it slippery, so that it slides through the intestine more easily. 4-It is not absorbed and increase the bulk of the intestinal contents as it reduces the water absorption **Liquid paraffin** ➢Used to prevent and treat fecal impaction. ➢Aspiration can result in a severe lipid pneumonitis ➢Long-term use can impair absorption of fat-soluble vitamins. ➢Can slip out of anal sphincter and causes embarrassment. ➢ Not recommended for regular use.

Osmotic Laxatives

Soluble but **nonabsorbable** compounds that result in increased stool liquidity due to an increase in fecal fluid

Nonabsorbable Sugars or Salts	Lactulose	Balanced Polyethylene Glycol
➢Magnesium hydroxide (milk of magnesia) Not used for prolonged periods in renal insufficiency due to the risk of hypermagnesemia. ➢Large doses of magnesium citrate & sodium phosphate cause Purgation: rapid bowel evacuation within 1-3 h. This might cause volume depletion.	➢**Disaccharide**, not absorbed causing retention of water through osmosis leading to softer, easier to pass stool. ➢in the colon, it is fermented by the gut flora producing osmotic metabolites causing severe flatus and cramps. ➢Drug of choice in **hepatic encephalopathy** to trap NH3. ➢Lactulose is converted into lactic acid, which decreases the luminal pH. So, NH3 is trapped and prevented from absorption (At low pH, NH3 is protonated into NH4+, which is a charged polar molecule that cannot cross plasma membranes and does not have a receptor, that how lactate traps ammonia)	➢Safe solution: no intrvascular fluid or electrolyte shifts. Does not cause cramps or flatus. ➢It is a laxative solution that increases the amount of water in the intestinal tract to stimulate bowel movements ➢**PEG is an inert, nonabsorbable, cosmetically active sugar** ➢It also contains Sodium sulfate, bicarbonate and potassium chloride to replace electrolytes that are passed from the body in the stool ➢used to clean the bowel before colonoscopy, a barium x-ray or other intestinal procedures. ➢For colonic cleansing, it is ingested rapidly (4L over 2-4 h). ➢For chronic constipation, PEG powder is mixed with water or juice.

Laxatives

Stimulant Laxatives				Opioid Receptor Antagonists	
➢Direct stimulation of the enteric nervous system and colonic electrolyte and fluid secretion.				➢Do not cross the BBB. ➢Block peripheral (μ) mu–opioid receptors without central analgesic effects.	
Anthraquinone Derivatives	**Bisacodyl**	**Phenolphthalein**	**Castor Oil**	**Methylnaltrexone**	**Alvimopan**
➢**Aloe**, **senna**, and **cascara** ➢Occur naturally in plants. ➢Poorly absorbed & after hydrolysis in the colon, produce a bowel movement in 6–12 h when given orally and within 2 h when given rectally. ➢**Chronic** use leads to a brown pigmentation of the colon known as "**melanosis coli.**"	➢ Tablet and suppository for treatment of acute and chronic constipation ➢ Induces bowel movement within 6–10 h orally and 30–60 minutes rectally. (At night) ➢ Safe for acute and long-term use	➢ Removed from the market owing to concerns about possible cardiac toxicity.	➢ Hydrolyzed in upper intestine into ricinoleic acid which is a local irritant. ➢ Was used as purgative to clean the colon before procedures.	➢ Used for opioid-induced constipation in patients with advanced illness and that are not responding to other agents, given as a subcutaneous injection every 2 days.	➢ Short-term use for postoperative ileus in hospitalized patients. ➢ Given orally within 5 hours before surgery and twice daily after surgery until bowel function has recovered, but for no more than 7 days, because of possible cardiovascular toxicity

Antidiarrheal Agents

*** Should not be used in patients with **bloody diarrhea**, **high fever**, or **systemic toxicity** because of the risk of worsening the underlying condition.
*** Used to control **chronic diarrhea** caused by **irritable bowel syndrome (IBS)** or **inflammatory bowel disease**.

<table>
<tr><th colspan="3">Opioid Agonists</th><th colspan="3">Bile Salt-Binding Resins</th><th>Octreotide</th></tr>
<tr><td colspan="3">➢Increase colonic transit time and fecal water absorption.
➢They also decrease mass colonic movements
➢CNS effects and potential for addiction limit the usefulness of most.</td><td colspan="3">–</td><td>➢Synthetic octapeptide with actions similar to somatostatin.</td></tr>
<tr><th>Loperamide</th><th>Diphenoxylate</th><th>Lomotil</th><th>Cholestyramine</th><th>Colestipol</th><th>Colesevelam</th><th>–</th></tr>
<tr><td>• Does not cross BBB, so No analgesic or addiction potential.</td><td>• Not analgesic in standard doses.

• Higher doses have CNS effects.

• Can cause dependence.</td><td>• Combination of small amounts of atropine and small doses of diphenoxylate

• contribute to the antidiarrheal action</td><td colspan="3">• Malabsorption of bile salts cause diarrhea. (Crohn's disease or after surgical resection).

• These drugs bind bile salts and decrease diarrhea caused by excess fecal bile acids

• Cholestyramine and colestipol reduce absorption of drugs and fat, but Colesevelam does not

• Side effects : Can cause bloating, flatulence, constipation and fecal impaction.</td><td>Clinical Uses:
1- Inhibition of endocrine tumor effects: Carcinoid and VIPoma (neuroendocrine tumors that secrete vasoactive intestinal polypeptide (VIP)) can cause secretory diarrhea, flushing and wheezing.
2- Diarrhea due to vagotomy or dumping syndrome (ingested foods bypass the stomach too rapidly) or short bowel syndrome and AIDS.
3- To stimulate motility in small bowel bacterial overgrowth or intestinal pseudo-obstruction secondary to scleroderma (a disease affecting the skin and other organs that is one of the autoimmune rheumatic diseases)
4- It inhibits pancreatic secretion, so used in patients with pancreatic fistula (leakage of pancreatic secretions from damaged pancreatic ducts).
5- treatment of pituitary tumors (e.g., acromegaly)
6- Sometimes used in gastrointestinal bleeding.</td></tr>
<tr><td colspan="6"></td><td>Adverse Effects:
➢Impaired pancreatic secretion may cause steatorrhea which can lead to fat-soluble vitamin deficiency.

➢Nausea, abdominal pain, flatulence, and diarrhea.

➢Formation of sludge or gallstones, due to inhibition of gallbladder contractility and fat absorption

➢Hyper or hypoglycemia due to hormonal imbalance.

➢Hypothyroidism

➢Bradycardia</td></tr>
</table>

THE END
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