GI Pharmacology Summary

Drug	Mechanism of action	uses	side effects	note
drugs used to neutralize or inhibit gastric sections				
• antacids	AL(OH)3 + HCl -----> ALCl3 + H2O 2HCl + Mg(OH)2 ----> MgCl2 + 2H2O	Nonprescription remedies for treatment of heartburn & dyspepsia.		Given 1 hour after a meal effectively neutralizes gastric acid for up to 2 hours.
Aluminum antacids			- constipation -interfere with absorption of many drugs.	
Magnesium antacids	have laxative action		diarrhea	ionic magnesium stimulates gastric release (acidrebound)
Magnesium trisilicate	slow-acting antacid			Combination of Magnesium & aluminum antacids are most commonly used (No diarrhea or constipation).
Calcium carbonate	2HCl + CaCO3 ---> CaCl2 + CO2 + H2O		with excessive chronic use, it may cause milk-alkali syndrome with elevation of serum calcium, phosphate , urea, nitrogen, creatinin & bicarbonate levels.	associated with "acid rebound"
Sodium bicarbonate	NaHCO3 + HCl → NaCl + H2O + CO2		-Highly absorbed, potentially causing metabolic alkalosis. - CO2 results in belching.	-Should be avoided as it counteracts diuretic therapy for hypertension. -Short duration of action, followed by acid rebound.

H2- Receptor Antagonists (Cimetidine Ranitidin Famotidine Nizatidine)	• Decrease secretion stimulated by: – Histamine. – Gastrin. – Acetylcholine. • Inhibit 60-70% of total 24-h acid secretion. – 90% of nocturnal acid. – 60% of day-time, meal stimulated, acid.	■**Gastroesophageal Reflux:** -Prophylactically, before meals. -Afford healing for erosive esophgitis in less than 50% of patients. – Proton pump inhibitors are preferred. ■ **Non Ulcer Dyspepsia**. ■**Stress Relateds-Gastritis:** – Can prevent bleeding, usually given IV. ■ **Peptic Ulcer Disease:** –Replaced by PPI. – Healing rate greater than 80-90% after 6-8 weeks. – Not effective in the presence of H. pylori infection. – Not effective if NSAID is continued.	Extremely safe drugs, but can (in 3% of patients) cause diarrhea, headache, fatigue, myalgia and constipation. ■ **CNS:** – Confusion, hallucinations occur only with IV cimetidine to elderly patients in ICU. ■ **Endocrine Effects:** – Again only with cimetidine, can inhibit estradiole metabolism, and can increase prolactin serum levels. ■ **Pregnancy and Nursing Mothers:** – Can cross placental barrier and appear in breast milk. ■ **Other Effects**: – Rarely can cause bradycardia and hypotension. **Drug Interactions:** - Cimetidine can inhibit cytochrome P450 Enzymes (CYP1A2,CYP2C9, CYP2D6, and CYP3A4), so can increase half life of many drugs. - Ranitidine binds 4-10 times less. - Nizatidine and famotidine binding is negligible	- Duration of action: 12 hours. - Cimetidine, Ranitidine, Famotidin first-pass metabolism bioavailability 50% . Nizatidine has little first-pass metabolism .

Proton Pump Inhibitors (PPI)	After intestinal absorption, they diffuse across lipid membranes into acidified compartments such as the parietal cell canaliculus. The prodrug becomes protonated and concentrated more than 1000-fold within the parietal cells. There, it undergoes a molecular conversion to the active form which covalently binds the H+/K+ ATPase enzyme and inactivates it.	■**Gastroesophageal Reflux (GERD):** They are the most effective agents in all forms of GERD and complications. ■ **Nonulcer Dyspepsia:** – Modest activity. – 10-20% more beneficial than a placebo ■ **Stress- Related Gastritis:** – Oral immediate-release omeprazole administered by nasogastric tube. – For patients without a nasoenteric tube, IV H2-antagonists are preferred because of their proven efficacy. ■ **Gastrinoma and other Hypersecretory Conditions:** Usually high doses of omeprazole are used. ■ **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 of the antibiotics. •**NSAID-associated ulcers:** PPIs promote ulcer healing despite continued NSAID use. Also used to prevent ulcer complications of NSAIDs. • **Rebleeding peptic ulcer:** -Oral or IV. -High pH may enhance coagulation and platelet aggregation.	Increased serum gastrin levels: Hyperplasia of ECL cells , Carcinoid tumors in rats, Increase proliferative rate of colonic mucosa, Chronic inflammation in gastric body, Atrophic gastritis and intestinal metaplasia. Drug Interactions: – May affect absorption of drugs due to decreased gastric acidity like digoxin and ketoconazole. – Omeprazole can inhibit metabolism of drugs such as diazepam and phenytoin. – Rabeprazole and pantoprazole have no significant interaction.	- Very efficacious and safe drugs. -They are lipophilic weak bases (pKa 4-5). -Should be given one hour before meal. -Have short half lives but effect lasts for 24 hours due to irreversible inhibition -Inhibit both fasting and meal-stimulated secretion because they block the final common pathway of acid secretion (90-98% of 24-hour secretion). - **treatment for Peptic Ulcer Disease:** Triple Therapy: # PPI twice daily. #Clarithromycin 500mg twice daily. #Amoxicillin 1gm twice daily ,OR, Metronidazole 500mg twice daily

omeprazole **Rabeprazole**				- both taken orally -Rabeprazole has immediate release omeprazole have faster onsets of action.
Lanzoprazole **Pantoprazole** **Esmoprazole**				- orally + IV
DRUGS AFFECTING GI MOTILITY				
Laxatives				Intermittent constipation is best prevented with(Nonpharmacologic Remedies): - high-fiber diet. - adequate fluid intake. - responding to nature's Call. - Regular exercise.
Bulk-Forming Laxatives	indigestible, hydrophilic colloids that absorb water, forming a bulky, emollient gel that distends the colon and promotes peristalsis.		Can cause bloating and flatus.	Common preparations include natural plant products (psyllium, methylcellulose, Sterculia ”Normacol”) and synthetic fibers (polycarbophil).
Stool Surfactant Agents (Softeners): **■ Docusate.** **■ Glycerin suppository.** **■ Mineral oil**	permit water and lipids to penetrate			given orally or rectally
Mineral oil	Clear viscous oil that lubricates fecal material, retarding water absorption from the stool.	Used to prevent and treat fecal impaction	- Aspiration can cause lipoid pneumonia. - Can impair absorption of fat-soluble vitamins.	

Osmotic Laxatives (Purgatives)	Soluble nonabsorbable compounds that result in increased stool liquidity due to an obligate increase in fecal fluid.			
Magnesium oxide (Milk of Magnesia)			Can cause hypermagnesemia. Large doses of magnesium citrate and sodium phosphate can cause Purgation: rapid bowel evacuation within1-3 hours. This might cause volume depletion.	
Lactulose			Sugars metabolized by bacteria producing severe flatus and cramps.	
Balanced Polyethylene Glycol		- Used for complete colonic cleansing before endoscopy . - For colonic cleansing, it should be ingested rapidly(4 L over 2-4hs). - For chronic constipation, PEG powder is mixed with water or juice.		- Safe solution: no intrvascular fluid or electrolyte shifts. Does not cause cramps or flatus. - PEG is an inert, nonabsorbable, osmotically active sugar. it contains Sodium sulfate, chloride, bicarbonate and potassium chloride to replace electrolytes that are passed from the body in the stool.
Stimulant Laxatives (Cathartics)	Direct stimulation of the enteric system and Colonic electrolyte and fluid secretion.	May be needed in neurologically impaired patients and in bed-bound patients in long term care facilities	Can lead to dependence and destruction of the myenteric plexus resulting in colonic atony and dilation.	

Anthraquinone Derivatives: **– Aloe.** **– Senna.** **– Cascara.**			Cause brown pigmentation of the colon" Melanosis Coli"	- Poorly absorbed - After hydrolysis, produce bowel movement in (6-12) hours.
Castor Oil	Hydrolyzed in upper intestine into ricinoleic acid	Was used as purgative to clean the colon before procedures	ricinoleic acid which is a local irritant	
Tegaseroid	serotonin 5-HT4 partial agonist The drug promotes gastric emptying and small and large bowel transit but has no effect on esophageal motility.Also stimulates cAMP-dependent chloride secretion leading to increased stool liquidity	- Chronic constipation. - Nonulcer dyspepsia. - Gastroparesis. - Irritable bowel syndrome(Approved for short term treatment of women with IBS who predominantly have constipation.)	- Diarrhea occurs in 9% of patients but resolves within days.	Extremely safe drug , but Expensive. - Reduces pain, bloating and hardness of stool.
Antidiarrheal Agents				
Loperamide	Opioid Agonists: Inhibit presynaptic cholinergic nerves, leading to increased colonic transit time and increased fecal water absorption. Decrease mass colonic movements and gastrocolic reflex.		Does not cross BBB. No analgesic or addiction potential	
Diphenoxylate	same as loperamide		Can have CNS effects and dependence	

Kaolin **Pectin**	act to absorb bacteria, toxins and fluid			**- Kaolin** is a naturally occurring hydrated magnesium silicate. **Pectin** is an indigestible carbohydrate derived from apples - Usually combined, e.g. Kaopectate. - Taken far from other medications
Cholestyramine **Colistipol**	bind bile salts		Can cause bloating, flatulence, constipation and fecal impaction. Also, drug and fat malabsorption	Malabsorption of bile salts (e. g .after surgical resection), can cause diarrhea.
Octreotide	synthetic octapeptide with actions similar to somatostatin	1. Inhibition of endocrine tumor effects: Carcinoid can cause secretory diarrhea and systemic symptoms like flushing and wheezing. 2. Diarrhea due to vagotomy or dumping syndrome or and AIDS. 3. In small doses can stimulate motility in small bowel bacterial overgrowth or intestinal pseudo-obstruction secondary to scleroderma. 4. pituitary tumors and GI bleeding		
Drugs used in Irritable Bowel Syndrome				
Dicyclomine **Hyoscyamine.**	Antispasmodic or Anticholinergic Agents ,They inhibit muscarinic cholinergic receptors in the enteric plexus and on smooth muscle		At usual low doses, have minimal side effects.	

Alosterone	Selective antagonist of 5-HT3 receptors		Can cause ischemic colitis, severe constipation requiring hospitalizationand surgery	– Has long duration of action. – Approved for women with severe IBS in whom diarrhea is the prominent symptom. – Efficacy in men is not established
Antiemetic Agents				
Ondansetron Granisetron	Block central 5-HT3 and peripheral (main effect) 5-HT3 receptors.	Prevention of acute chemotherapy-induced nausea and emesis and postoperative nausea and vomiting	Headache, dizziness, and constipation	- Serotonin 5-HT3 Antagonists - Prevent emesis due to vagal stimulation and chemotherapy. Other emetic stimuli such as motion sickness are poorly controlled. - Their efficacy is enhanced by combination therapy with dexamethasone and NK1-receptor antagonist
Aprepitant	Block central NK1receptors in the area postrema	Used in combination with 5-HT3-receptor antagonists and corticosteroids for the prevention of acute and delayed nausea and vomiting from chemotherapy		Neurokinin 1 Receptor (NK1) Antagonists
Dronabinol Nabilone	not understood.	Used for chemotherapy-induced vomiting	Euphoria, dysphoria, sedation, hallucinations, dry mouth, and increased appetite	Cannabinoids (Psychoactive agents.)
Prochlorperazine Promethazine Droperidol	Antiemetics due to blocking dopamine and muscarinic receptors.		Sedative effects due to antihistamine activity.	Antipsychotic drugs

Lorazepam Diazepam		Reduce vomiting caused by anxiety		
Antiprotozoal drugs				
luminal amebicide		-Treatment of Asymptomatic Ameba Intestinal Infection (asymptomatic carries) -Therapy with a luminal amebicide is also required in the treatment of all other forms of amebiasis		
	• miscellaneous antiprotozoals			
Metronidazole (Flagyl, Metrogel)	•The enzyme, pyruvate-ferredoxin oxidoreductase, found only in anaerobic organisms, reduces metronidazole and thereby activates the drug. • Reduced metronidazole disrupts replication and transcription and inhibits DNA repair.	Drug of choice in the treatment of: - Extraluminal amebiasis - all tissue infections with E histolytica. (hepatic abscess; intestinal wall/ extraintestinal infections) - Giardiasis Efficacy after a single treatment is about 90% Tinidazole is equally effective. - Trichomoniasis A single dose of 2 g is effective.	<u>Common:</u> Nausea, headache, dry mouth, metallic taste. Infrequent adverse effects: vomiting, diarrhea, insomnia, weakness, dizziness,. <u>Rare:</u> Pancreatitis and severe central nervous system toxicity	- In addition to its use as antiprotozoals it also used for treating bacterial infections (not penetrates mammalian cells) - Not effective against luminal parasites and so must be used wit a luminal amebicide to ensure eradication of the infection.It kills trophozoites but not cysts - Metronidazole is best avoided in pregnant or nursing women, although congenital abnormalities have not clearly been associated with use in humans.
tinidazole	Same MOA as metronidazole		-Same as metronidazole but is better tolerated and has better toxicity profile	it can be given in a single dose

nifuratel				can be used as an alternative to metronidazole or tinidazole in the treatment of trichomoniasis
	• Antimalarial Drugs (Chloroquine , Quinine , Artemisinin, Doxycycline , Pyrimethamine)			
Chloroquine		Most useful agent to terminate an acute attack	N,headache, and is teratogenic	- Available as oral, IV, and IM preparation - Resistance develops
Quinine				– Oldest drug, from Cinchona tree. – Many actions – Toxic – Still used, no resistance to its action
Artemisinin				New drug, from Sweet wormwood
Anthelmintics				
Anthelmintics	are drugs that act either locally to expel worms from the gastrointestinal tract or systemically to eradicate adult helminths or developmental forms that invade organs and tissues			exert their antiparasitic effects by interference with (1)energy metabolism, (2)neuromuscular coordination, (3) microtubular function, (4) cellular permeability
Piperazine (Vermizine)	- It acts on the musculature of the helminths to cause reversible flaccid paralysis mediated by chloride-dependent hyperpolarization of the muscle membrane. this results in expulsion of the worm.	Treatment for infections caused by Nematodes		-Prolonged treatment and might need a purgative - contains a heterocyclic ring that lacks a carboxyl group.

	- Piperazine acts as an agonist at gated chloride channels on the parasite			
Diethylcarbamazine	It interferes with the metabolism of arachidonic acid and blocks the production of prostaglandins, resulting in capillary vasoconstriction and impairment of the passage of the microfilaria	Treatment for infections caused by Nematodes		
Mebendazole (Vermox)		Treatment for infections caused by Nematodes		- safe drug. •Threadworm: Enterobius vermicularis, simple treatment: single dose, can be repeated after 3 weeks. •Hockworm: Ankylostomiasis: 2tablets*3days. •Roundworm: Ascaris lumbricoid
Niclosamide	amchlorinated salicylamide that inhibits the production of energy derived from anaerobic metabolism. Inhibition of anaerobic incorporation of inorganic phosphate into ATP is detrimental to the parasite.	Treatment for infections caused by Cestodes		The drug affects the scolex and proximal segments of the cestodes,resulting in detachment of the scolex from the intestinal wall and eventual evacuation of the cestodes from the intestine by the normal peristaltic action of the host's bowel.

Praziquantel (Biltricide)	neuromuscular effects appear to increase parasite motility leading to spastic paralysis. The drug increases calcium permeability through parasite-specific ion channels, so that the muscle cells of the parasite accumulate calcium This action is followed by exposure of hitherto masked tegmental antigens, lipid anchored protein, and actin. Insertion of the drug into the fluke's lipid bilayer causes conformational changes, rendering the fluke susceptible to antibody- and complement-mediated assault.	Treatment for infections caused by Trematodes		

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