GIT Pharmacology Summary

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Lecture 1: Proton pump inhibitors

Drug Name	Classification	Action	MOA	Indications	ADRS	C.I	Notes
Omeprazole Lansoprazole Pantoprazole Raprazole	Proton Pump Inhibitors (PPIs)	Marked inhibition of basal & meal stimulated-acid secretion. Reduce pepsin activity. Promote mucosal healing & decrease pain.	Irreversible inhibition of proton pump (H+/ K+ATPase)	1) Eradication of H. pylori *(combined with antimicrobial drugs).* 2) Resistant severe peptic ulcer. 3) GERD. 4) Hypersecretory conditions as Zollinger Ellison syndrome and gastrinoma (First choice).	**long term use may lead to:** - Achlorhydria *(absence HCl.* - Hypergastrinemia *(hyperplasia of the parietal cells).* - Gastric mucosal hyperplasia. - Increased bacterial flora. - Vitamin B12 and iron deficiency. - Decrease calcium absorption. - Longer use may lead to hip fractures.	**Should not be combined with H 2 blockers or antacids**	- The most potent inhibitors of acid secretion. - Proton pump inhibitors heal ulcers faster than H2 blockers. - Bioavailability reduced by food (given on empty stomach) - Omeprazole is a very potent liver enzyme inhibitor can interact with other drugs such warfarin and **Clopidogrel activation (antiplatelet)**
Cimetidine Ranitidine Famotidine Nizatidine	H2 receptor blockers	- Reduce basal and food stimulation-acid secretion. - Reduce pepsin activity.	They reversibly and competitively block H2 receptors on the parietal cells.	- Nocturnal GERD. - Pre-anesthetic to prevent aspiration. - Post–ulcer healing maintenance therapy.	- Cimetidine is a CYT-P450 inhibitor leading to decrease warfarin metabolism. - Gynecomastia & impotence) due to inhibition of dihydrotestosterone binding to androgen receptors	- Dose reduction of H2 receptor blockers in severe renal or hepatic failure and elderly	- Famotidine is the most potent drug. - Exposed to first pass metabolism (except nizatidine that has the greatest bioavailability)
Misoprostol	Prostaglandin analogues	- Decrease HCL secretion - Increase protective measure		Used for NSAIDS-induced peptic ulcer.	Uterine contraction (dysmenorrhea or abortion)		Can cause vaginal bleeding
$NaHCO_3$	Antacids		Direct chemical neutralization of HCL, as a result, may decrease pepsin activity		systemic alkalosis	Contraindicated in CVS patients	*inorganic salts* they **decrease absorption of some drugs as tetracycline, fluoroquinolones, iron**.
$CaCO_3$					- Milk-alkali syndrome -Hypercalcemia may lead to Renal failure		
$Al(OH)_3$					Constipation & systemic phosphate depletion causing weakness, malaise and anorexia.		
$Mg(OH)_2$					Diarrhea		

Lecture 2: Anti-Emetics

Drug Name	Classification	Action	Indications	ADRS
Ondansetron Granisetron	5-HT3 antagonists	**First choice for moderate to severe emesis induced by:** -Chemotherapy-induced nausea and vomiting especially cisplatin. -Post-radiation NV & Post-operative NV. -Their effects is augmented by combination with corticosteroids and NK1 antagonists.		*They are well tolerated (minimal side effects). -Headache, dizziness and constipation. -Minor ECG abnormalities (QT prolongation).
Domperidone Metoclopramide	Prokinetic D2 receptor antagonists	**Mechanism:** blocking D2 receptors in CTZ, 5HT4 agonist activity **Action:** increased upper GI motility & gastric emptying.	-GERD. -Gastroparesis. -Cytotoxic induced vomiting.	**<u>Because Metoclopramide do cross BBB it causes:</u>** - Dyskinesia, Galactorrhea, menstrual disorders, impotency, Postural hypotension, Sedation and drowsiness *REMEMBER: Domperidone doesn't cross BBB.
Chlorpromazine Droperidol	Neuroleptic D2 receptor antagonists	-	-Postoperative vomiting -Chemotherapy-induced emesis.	-Extra pyramidal symptoms -Sedation -Postural hypotension
Aprepitant	Neurokinin1 (NK1) receptor antagonists	Acts centrally as substance P antagonist by blocking neurokinin 1 receptors in vagal afferent fibers.	**NOTE**: Usually combined with 5-HT3 antagonists and corticosteroids in prevention of chemotherapy-induced nausea and vomiting and post- operative NV.	
Diphenhydramine Promethazine Meclizine Cyclizine	H1 receptor antagonists	-Meclizine and Cyclizine do have teratogenic effect. (contraindicated in pregnancy)	-Motion sickness -Morning sickness in pregnancy -Promethazine: severe morning sickness of pregnancy **(if only essential)**	-Prominent sedation -Hypotension -Anticholinergic effects or atropine like actions (dry mouth, dilated pupils, urinary retention, constipation).
Hyoscine (scopolamine)	Muscarinic receptor antagonists	Reduce impulses from vestibular apparatus	Used as transdermal patches in motion sickness (applied behind the external ear).	-Sedation, Tachycardia, blurred vision, dry mouth, constipation, urinary retention (atropine-like actions). **NOTE:** -Not in chemotherapy induced vomiting.
Dexamethasone Methylprednisolone	Glucocorticoids	Used in chemotherapy-induced vomiting	**NOTE**: combined with 5-HT3 antagonists or NK1 receptor antagonists.	Side effects in long term use: Hyperglycemia, Hypertension, Cataract, Osteoporosis, Increased intraocular pressure, Increased susceptibility to infections, Increased appetite & obesity

Lecture 3: Treatment of dysentery and amoebiasis

Drug Name	Classification	Actions	Indications	ADRS	C.I	Notes
Metronidazole Tinidazole	Systemic amebicides	-Treating invasive amebic infections (intestinal & extra-intestinal amebiasis). **Mechanism**: -Inhibits DNA replication. -Does not eradicate cysts from intestine	-Drug of choice in all extra-luminal amebiasis. -Giardiasis. -Peptic ulcer (H. Pylori) -Pseudo-membranous colitis.	-Metallic taste. -Oral Thrush. -Dysuria, dark urine. -Disulfiram-like effect if taken with alcohol convulsion.	-Pregnancy and breast-feeding women. -Alcohol intake. -CNS diseases. -Severe renal disease. -Severe hepatic disease.	**Drug Interactions**: increases anticoagulant effect of warfarin. Increases lithium toxicity. Tinidazole is the better drug.
Emetine and dehydroemetine		**Mechanism**: Effective against tissue trophozoites of E. histolytica causing irreversible block of protein synthesis.	-Amoebic liver abscess. -Intestinal wall infections. -Severe forms of amebiasis acute amoebic dysentery.	Cardiotoxicity: Hypotension, cardiac arrhythmias, heart failure.	-Should not be used in patients with cardiac or renal disease, in young children, or pregnancy.	Dehydroemetine is preferable due to less toxicity
Chloroquine		Anti-malarial drug.	-Combination with metronidazole or dehydroemetine for amebic liver diseases	-Pruritus is common. -Blurring of vision. -Hemolysis in G6PD deficient patients.		Must be taken with food to avoid NVD & because of its bitter taste
Diloxanide furoate	Luminal Amebicides	-The unabsorbed diloxanide is the amoebicidal agent. -***MECHANISM is** Unknown	-Drug of choice for asymptomatic intestinal infection (cysts passers). -After treatment of invasive systemic amebicides	Flatulence	-Pregnancy -Children (less than 2 years).	Direct amoebicidal action against luminal forms Not active against trophozoites in intestinal wall or extra-intestinal tissues.
Iodoquinol		Effective against the luminal forms of amebiasis -***MECHANISM is** Unknown	Luminal amoebicide for asymptomatic amebiasis	-Optic neuritis -Enlargement of the thyroid gland.	-Optic neuropathy. -Thyroid disease.	discontinued if it produces persistent diarrhea or signs of iodine toxicity.
Paromomycin Sulphate		-Has direct amebicidal action (causes leakage by its action on cell membrane of parasite). -Indirect killing of bacterial flora essential for proliferation of pathogenic amoebae.	-Chronic amebiasis to liminate cysts.	-Gastrointestinal distress and diarrhea	-Severe renal disease -Patients with GIT ulceration	
Ciprofloxacin	Bacillary Dysentry	Block bacterial DNA synthesis	Bacterial diarrhea (caused by shigella, salmonella and E. coli).	-Phototoxicity. -Arthropathy (damage of growing cartilage).	-Children, pregnancy, nursing mother. -Epilepsy. -Arrhythmias. -Should not be combined with antacids, divalent cations.	Cotrimoxazole in traveler's diarrhea.
Ceftriaxone & Cefixime		Act by inhibiting cell wall synthesis	In case of children or patient allergic to sulfonamides, cephalosporins can be used.			

Lecture 4: Drugs used in IBD

Drug Name	Classification		Action & Mechanism	Indications	ADRS	Notes
Sulfasalazine Balsalazide Olsalazine	**Aminosalicylate**	**Azo compounds**	-In the terminal ileum and colon, azo bond is cleaved by azoreductase enzyme releasing 5-ASA. -Anti-inflammatory action due to: • inhibition of prostaglandins and leukotrienes. • decrease neutrophil chemotaxis. • Antioxidant activity	• Induction and maintenance of remission in mild to moderate IBD (First line of treatment). • Rheumatoid arthritis (Sulfasalazine only). • Rectal formulations are used in distal ulcerative colitis, ulcerative proctitis and proctosigmoiditis.	• Crystalluria. • Bone marrow depression • Megaloblastic anemia. • Folic acid deficiency (should be provided). • Impairment of male fertility (Oligospermia). • Interstitial nephritis due to 5-ASA.	We are only talking about Sulfasalazine here.
Asacol		**Mesalamine**	5-ASA coated in pH-sensitive resin that dissolve at pH 7.		-	**<u>Sulfa free useful in patients sensitive to sulfa drugs.</u>**
Pentasa			micro granules that release 5-ASA throughout the small intestine.			
Canasa			Rectal Suppository.			
Rowasa			Rectal Enema.			
prednisone, prednisolone (Oral)	**Glucocorticoids**		• Inhibits phospholipase A2 • Inhibits gene transcription of NO synthase, cyclo-oxygenase-2 (COX-2) • Inhibit production of inflammatory cytokines	Indications ONLY: • acute flares of disease (moderate –to- severe active IBD). • Oral glucocorticoids are commonly used in active condition. • Rectal glucocorticoids are preferred in IBD involving rectum or sigmoid colon. • Asthma • Rheumatoid arthritis • immunosuppressive drug for organ transplants • Antiemetic during cancer chemotherapy		-Parenteral > oral > Rectal in terms of absorption. -Rectal has minimal side effects and maximum tissue effects. -Budesonide: Is subjected to extensive first pass metabolism
hydrocortisone, methyl prednisolone (IV)						
Hydrocortisone (rectal)						
Budesonide(synthesized)						
Methotrexate	**Immunomodulators**		• Impairs DNA synthesis • Inhibits dihydrofolate reductase required for folic acid activation.	• Inflammatory bowel disease • Rheumatoid arthritis • Cancer	• Megaloblastic anemia • Bone marrow depression	-Used to induce & maintain remission of IBD. -Moderate-to-severe conditions or steroid dependent or steroid resistant.

Drug Name	Classification	Action & Mechanism	Indications	ADRS	Notes
Azathioprine & 6-Mercaptopurine	**Immunomodulators: Purine analogs**	Inhibit purine synthesis and inhibits synthesis of DNA, RNA, and proteins.	Induction and maintenance of remission in IBD	• Bone marrow depression: leucopenia, thrombocytopenia. • Gastrointestinal toxicity. • Hepatic dysfunction. Complete blood count & liver function tests are required in all patients	
Infliximab	**Monoclonal antibodies**	Inhibits soluble or membrane – bound TNF-α located on activated T lymphocytes.	• In moderate to severe active Crohn's disease and ulcerative colitis. • Patients not responding to immunomodulators or glucocorticoids. • Treatment of rheumatoid arthritis • Psoriasis	• Acute or early & delayed adverse infusion reactions • Infection complication • Loss of response to infliximab over time due to the development of antibodies to infliximab. • Severe hepatic failure.	• 2 weeks to give clinical response • Pretreatment with diphenhydramine, acetaminophen, corticosteroids is recommended.
Adalimumab		It binds to TNFα, preventing it from activating TNF receptors.			Given by subcutaneous injection
Certolizumab		Certolizumab is attached to polyethylene glycol to increase its half-life in circulation	Crohn's & rheumatoid Only.		

Lecture 5: Drugs used in constipation & IBS

Drug Name	Classification	Action	Mechanism	Indications	ADRS	C.I	Notes
Hydrophilic colloids: 1-Methyl cellulose 2-Carboxymethyl 3-Cellulose (CMC)	Bulk forming Laxatives	Dietary fibers and hydrophilic colloids are non absorbable substances they Increase the bulk of the intestinal contents by water retention → ↑ mechanical pressure on the walls of the intestine stimulation of stretch receptors → ↑peristalsis → evacuation of soft stool.		Constipation	-Intestinal obstruction (should be taken with enough water). -Interfere with other drug absorption e.g. iron, cardiac glycosides.		Include: -Dietary fibers indigestible: parts of vegetables & fruits -Bran powder
Sugars: -lactulose	Osmotic Laxatives	-Water soluble compounds -Poorly absorbable compounds (salts or sugars) -They remain in the bowel then attracts and retains water by osmosis thereby increasing the volume of feces → ↑ peristalsis → evacuation of stool.	In colon, metabolized by bacteria into fructose and galactose that are fermented into lactic acid thus, lowering the pH causing water retraction.	-Prevention of chronic constipation. -Hepatic encephalopathy. -Hemorrhoids.	-Delayed onset of action (2-3 days) -Abdominal cramps and flatulence. -Electrolyte disturbances.		Lactulose increases the H+ concentration in the gut, this favors the formation of the non-absorbable NH4+ from NH3, trapping NH3 in the colon and reducing its back diffusion into blood.
Salts (saline): -Magnesium sulphate or hydroxide. -Sodium or potassium phosphate.			Increase evacuation of watery stool. Magnesium sulphate (Epson's salt). Magnesium hydroxide (milk of magnesia). Sodium phosphate or potassium phosphate.	-Treatment of acute constipation WITH PLENTY of water	-Disturbance of fluid and electrolyte balance -May have systemic effects.	-Sodium salts are C.I in congestive heart failure. -Magnesium salts are contraindicated in: *Renal failure, Heart block, CNS depression & Neuromuscular block* **NOTES:** -Have rapid effect (within 1-3 h). -Isotonic or hypotonic solution should be used.	
Polyethylene glycol (PEG)			-Isotonic solution of polyethylene glycol & electrolytes (NaCl, KCl, Na bicarbonate). -Used for whole bowel irrigation prior to colonoscopy or surgery (4L over 2-4 hours). -Limited fluid or electrolyte imbalance. (advantage) -Less flatulence and cramps. (advantage)				
Bisacodyl	Stimulant Laxatives	act via direct stimulation of enteric nervous system → increased peristalsis & purgation.	Given orally and it acts on colon.				Are the most powerful group among laxatives and should be used carefully.
Castor oil			-Given orally and it acts on small intestine. -Vegetable oil degraded by lipase → ricinoleic acid + glycerin -Ricinoleic acid is very irritating to mucosa.				
Anthraquinone derivatives: ***(senna, cascara, aloes)***			-Given at night and it acts on colon. -Hydrolyzed by bacterial colon into sugar + emodin (The absorbed emodin has direct stimulant action). -Emodin may pass into milk.		-Prolonged use → dependence & destruction of myenteric plexus leading to atonic colon. -Senna is contraindicated in breast feeding. -Castor oil is C.I. in pregnancy → reflex contraction of uterus → abortion		
Docusate Paraffin oil Glycerin	Fecal Softeners (Lubricants)/ surfactants	**Docusate:** Act by decreasing surface tension of feces	Paraffin oil: Is a mineral oil and given orally, Acts as lubricant thus softening the feces and promoting defecation, Good for radiology preparation, Not palatable & impairs absorption of fat soluble vitamins. Glycerin: Lubricant Given rectally (suppository)				

Lecture 5: Drugs used in constipation & IBS

Drug Name	Classification	Action & Mechanism	Indications	ADRS, C.I & Notes
Mebeverine	Antipasmodics		IBS	
Amitriptyline	Tricyclic antidepressants	-Anticholinergic action. -Reduce visceral afferent sensation.	IBS	
Alosetron	Selective 5HT3 antagonist	5-HT3 receptors antagonism of the enteric nervous system of the gastrointestinal tract results into: -Inhibition of colon motility. -Inhibition of unpleasant visceral afferent pain sensation (nausea, pain, bloating).	Used in IBS with severe diarrhea in women who have not had success with any other treatment.	Constipation and ischemic colitis may occur **NOTE:** People taking alosetron must sign a consent form before starting to take the medicine.
Tegaserod	$5HT_4$ agonist	Stimulation of $5HT_4$ of enteric nervous system of GIT $\rightarrow$ increases peristalsis.	Short term treatment of IBS-associated with constipation in **women <55 years old with no history of heart problems.**	Tegaserod has CVS side effects

Lecture 6: Cytochrome System

Cyp450 Isoform	Substrate		Inducer	Inhibitor	
3A4	• Fluconazole • Erythromycin • Clarithromycin	• Cyclophosphamide • Tamoxifen • Cyclosporine	• Barbiturates • Carbamazepine • Dexamethasone • Rifampicin	• Fluconazole • Ketoconazole • Itraconazole	• Ritonavir • Cimetidine • Cyclosporine
	• Astamizole • Midazolam • Clonazepam	• Amlodepine • Verapamil • Atorvastatin	• Rifabutin • Phenytoin • Progestins • Ritonavir	• Erythromycin • Clarithromycin • Troleandomycin	• Chloramphenicol • Nefazadone • Grape Fruits
2C9	• NSAIDs • S-warfarin • Phenytoin • Tolbutamide		• Baribturates • Rifampicin	• Fluconazole • Sulfphenazole	
2C19	• Diazepam • Omeprazole • Phenytoin		• Barbiturates • Rifampicin	• Omeprazole • Isoniazid • Paroxetine • Ketoconazole	

Side Notes:

Cyp450 2D6 → Heart Drugs & most frequent Polymorphism

Cyp450 1A2 → Smoking

Lecture 7: Hepatotoxic drugs

<table>
<tr><th colspan="2">Type of hepatotoxicity</th><th>Drugs</th><th>Mechanism</th><th>Latency</th></tr>
<tr><td rowspan="2">Direct</td><td>Dose dependent</td><td>• Acetaminophen
• Statins
• Salicylates
• Alcohol</td><td>Increasing the dose causes and increase in toxicity</td><td>The metabolite of the offending drug interferes with hepatic metabolism as that of bilirubin or protein synthesis…etc</td></tr>
<tr><td>Cumulative</td><td>• Amiodarone
• Oral Contraceptives
• Methotrexate
• Alcohol</td><td>taking it over a long period of time causes toxicity</td><td>INTERMEDIATE, but may continue to evoke even after drug</td></tr>
<tr><td rowspan="3">Indirect</td><td rowspan="2">Immuno-allergic</td><td>Drugs causing Inflammatory cholestasis:
• Chlorpromazine
• Chlorpropamide
• Erythromycin</td><td rowspan="2">A drug or its metabolite binds to hepatic membranes or proteins → act as hapten to induce a variety of immune reactions.</td><td rowspan="2">INTERMEDIATE, but may continue to evoke even after drug</td></tr>
<tr><td>Drugs causing viral Hepatitis-like pattern:
• Isoniazid
• Phenytoin
• methyldopa</td></tr>
<tr><td>Metabolic</td><td>Drugs that interfere with <u>bilirubin</u> metabolism:
• Erythromycin
• Rifampicin

Drugs that interfere with <u>protein</u> synthesis:
• Corticosteroids
• Tetracycline</td><td>The metabolite of the offending drug interferes with hepatic metabolism as that of bilirubin or protein synthesis…etc</td></tr>
</table>

Lecture 7: Hepatotoxic drugs

Clinical Manifestations of Toxicity	Underlying mechanism	Symptoms		Drugs inducing this condition	Treatment
Asymptomatic	**Increase in LFTs**	-		• Phenytoin • Statins • Sulfonamides • Sulfonylureas	1st step: Immediate withdrawal of any suspected drug. **Symptomatic:** If a severe allergic reaction is observed (Corticosteroids) If pruritus → enhance bile acid excretion (Cholestyramine) If cholestatic liver injury Ursodeoxycholic acid (Ursodiol) **Specific antidotes:** **For Acetaminophen toxicity → N-acetylcysteine** For Valproate toxicity → L-carnitine
Symptomatic	**Injury of hepatocytes (Hepatocellular)**	• rapid onset of malaise • severe anorexia • jaundice • Flu-like symptoms	• Diarrhea • urine discolored • **3 fold Increase in alanine aminotransferases (ALT).** • Normal level of ALP	• Acetaminophen • NSAIDs • Isoniazid • Amiodarone	
	injury of biliary system (cholestasis)	• develop jaundice • **severe pruritis** • dark urine	• stool may be light, hyperbilirubinaemia • 2 fold Increase in a (ALP) • Normal level of ALT	• Chlorpropamide • Erythromycin • Rifamycin • Oral contraceptives	
	Injury in both hepatocytes & biliary system (MIXED TYPE)	• 3-fold increase in ALT • 2-fold increase in ALP		• Phenytoin • Carbamazepine • Sulfonamides • ACE Inhibitors	

Lecture 8: Anti Coagulants

Drug Name	Classification	Action & Mechanism	Indications	ADRS	Notes
Unfractionated Heparin (UFH)	Indirect Thrombin Inhibitor	It **acts indirectly** by increasing the activity of the endogenous anticoagulant **Antithrombin III** (1000 folds) which inhibits activated clotting factors mainly thrombin (**factor** 2a) and **Xa**	• **Heparin does not cross the placenta; therefore, it is the drug of choice as anticoagulant during pregnancy** • used to **initiate immediate anticoagulation** in thromboembolic disease (PE, DVT, MI) in emergency conditions, mainly as induction for oral vitamin K antagonists (VKAs) • **Prevention of postoperative DVT** (in patient undergoing hip replacement) • Prevention of coagulation during renal dialysis or cardiac surgery	• Heparin-induced thrombocytopenia (HIT) • **Bleeding** • **Allergic reactions** • Long-term therapy **osteoporosis** Contraindicated in patients with: • hypersensitivity to the drug • Recent surgery of the brain, eye or spinal cord • threatened abortion	• **Not injected IM as it causes hematomas at injection site** • Close monitoring of the activated partial thromboplastin time (aPTT) is necessary in patients receiving UFH • Heparin is strongly acidic and is neutralized by IV protamine sulfate (a strongly basic protein) • Variable anticoagulant response
Low-Molecular-Weight **Heparins** (LMWH)		LMWHs increase the action of antithrombin III on factor Xa 10 ***but not its action on thrombin,*** because the molecules are too small to bind to both the enzyme and the inhibitor	• Are used increasingly in place of UFH	• Have equal efficacy • **without frequent laboratory monitoring** • Binding to platelets and osteoblasts is **reduced** with LMWH compared with UFH, so it will not cause osteoporosis or HIT • Predictable anticoagulant response	

Lecture 8: Anti Coagulants

Drug Name	Classification	Action & Mechanism	Indications, ADRS & Notes
Fondaparinux	Synthetic Heparin Derivatives	A synthetic compound that inhibits factor Xa 10 by antithrombin but **does not inhibit thrombin**	• Fondaparinux can be given once a day at a fixed dose without coagulation monitoring • Less likely than UFH or LMWHs to trigger HIT
Hirudin Lepirudin	Direct Thrombin Inhibitors	DTIs exert their anticoagulant effect by direct binding to thrombin	**Recombinant** hirudin "Lepirudin" is used as IV anticoagulant in patients with HIT.
Warfarin	Vit.K Antagonists	Inhibits synthesis of biologically active forms of Vitamin K-dependent coagulation factors II, VII, IX & X as well as anticoagulant proteins C & S	**Drug interactions increasing the effect of warfarin:** • Inhibition of Vit. K synthesis by intestinal flora; oral antibiotics • Inhibition of Vit K absorption liquid paraffin. • Decrease in drug metabolism by microsomal enzyme inhibitors **chloramphenicol, & cimetidine** • Displacement of the drug from protein binding sites; phenylbutazone & salicylates • Co-administration of drugs that increase bleeding tendency by inhibiting platelet function NSAIDs & heparin. **Drug interactions Decreasing the effect of warfarin:** • Inhibition of drug absorption from GIT; **cholestyramine, colestipol.** • Increase in synthesis of clotting factors; **Vit.K, oral contraceptives.** • Increase in drug metabolism by microsomal enzyme inducers **Carbamazepine, barbiturates& rifampicin** **C.I. during pregnancy because it can cause:** • Abortion &**Teratogenicity** • **Monitoring anticoagulant effect of warfarin by measuring PT, which is expressed as an International Normalized Ratio (INR)** • **Slow Onset** • **Narrow therapeutic window** **If the patient develops Bleeding due to Warfarin:** • **Stop the drug & IV injection of vitamin** K

Lecture 9: Anti Platelets

Drug Name	Classification	Action & Mechanism	Indications	ADRS	Notes
Aspirin	**Arachidonic acid pathway inhibitors**	• **Irreversible** inhibition of **cyclooxygenase enzyme** (COX-1) via acetylation. • Small dose inhibits **thromboxane** (TXA2) synthesis in platelets. But not **prostacyclin** (PGI_2) synthesis in endothelium (larger dose).	• **Prophylaxis of thromboembolism e.g.** prevention of transient ischemic attack, ischemic stroke and myocardial infarction. • **Prevention of ischemic events** in patients with unstable **angina pectoris.** • can be combined with other antiplatelet drugs (clopidogrel) or AntiCoag(heparin)	• Risk of peptic ulcer. Because it inhibits prostaglandin synthesis • Increased incidence of GIT bleeding (**aspirin prolongs bleeding time**)	
Ticlopidine **Clopidogrel**	**ADP pathway inhibitors**	**irreversibly** inhibit ADP receptor of subtype **P2Y12**	• Secondary prevention of ischemic complications after myocardial infarction, ischemic stroke and unstable angina.	• Sever neutropenia, CBC should be done monthly during treatment. Notes: • **pro-drugs**, • **inhibit CYT P450** causing **increased plasma levels** of drugs such as phenytoin and carbamazepine. **Clopidogrel:** • more potent & **Less side effects &** Bioavailability is unaffected by food. Clopidogrel has replaced ticlopidine for patients with: • history of **recent MI** , **Recent stroke**, **established peripheral arterial disease.** • **Acute coronary syndrome**	
Prasugrel **Ticagrelor**	**New ADP Pathway Inhibitors**			• Increased risk of bleeding • **Dyspnea (ticagrelor)**	• More rapid onset than Clopidogrel • Both drugs do not need hepatic activation.
Abciximab	**Glycoprotein IIb/ IIIa receptor inhibitors**	inhibits platelet aggregation by preventing the binding of fibronigen, von Willebrand factor, and other adhesive molecules to **GPIIb/IIIa** receptor sites on activated platelets.	• Used with heparin and aspirin as adjunct to PCI for the prevention of cardiac ischemic complications.		• I.V. • Glycoprotein IIb/ **IIIa receptor is required for platelet aggregation with** fibrinogen, von Willbrand factor & each other.
Tirofiban **Eptifibatide (peptide)**		Act by occupying the site on glycoprotein IIb/ IIIa receptor that is required to bind the platelet to fibrinogen **(act as fibrinogen- mimetic agents)**.	• Used for the reduction of incidence of thrombotic complications during coronary angioplasty (PCI)		
Dipyridamole	**Phosphodiesterase Inhibiter**	It is a **vasodilator.** **Inhibits phosphodiestrase** thus increases cAMP and decreases synthesis of thromboxane A2 and other platelet aggregating factors.	• Adjunctive therapy with warfarin for cardiac valve replacement • Secondary prevention of stroke and transient ischemic attack with aspirin	• Headache • Severe Postural hypotension	

Lecture 10: Anti-Malarial Drugs

Drug Name	Action & Mechanism	Indications	ADRS & Notes	
Artemesinin	Irreversibly bind & inhibit sarco-endoplasmic reticulum Ca2+- ATPase of the parasite, thereby inhibiting its growth Inhibiting formation of transport vesicles → no food vacuoles	Monotherapy should be extended beyond disappearance of parasite to prevent recrudescence By combining the drug with long-acting antimalarial drug	• Transient heart block • Decrease neutrophil count • Brief episodes of fever	Biotransformed in liver into dihydroartesiminin Artemisin-based combination therapies (ACTs): Artemether + lumefantrine Artemether + amodiaquine Artemether + mefloquine Artemether + sulfadoxine - pyrimethamin
Chloroquine	Prevents polymerization of heme to hemozoin by inhibition of hemepolymerase. Leading to accumulation of heme that results in lysis of the parasite and rbc.	• Safe in pregnancy • Potent blood Schizontocide • Active against all forms of the schizonts • Used to eradicate blood schizonts of Plasmodium • Hepatic amoebiasis • Rheumatoid arthritis	Therapeutic use: Mild headache and visual disturbances, GI upsets, Pruritus, urticaria. Prolonged therapy: Ocular toxicity: Loss of accommodation, lenticular opacity, retinopathy, ototoxicity Weight loss Bolus injection leads to hypotension & dysrhythmias. Resistance against the drug develops because of mutation of the chloroquine resistance transporter (PfCRT) which enhances the efflux of chloroquine from the food vacuole.	
Quinine	Same as ^	• Parenteral treatment of severe falciparum malaria • Oral treatment of falciparum malaria • Nocturnal leg cramps	**Therapeutic dose**: poor compliance → bitter taste. **Higher doses:** • Cinchonism: (tinnitus, deafness, headaches, nausea & visual disturbances) Abdominal pain & diarrhea. Hypotension & arrhythmias, hypoglycemia Rashes, fever, hypersensitivity reactions • Blood dyscarasis; anaemia, thrombocytopenic purpura & hypo prothrombinaemia. • Blackwater fever, a fatal condition in which acute haemolytic anaemia is associated with renal failure	• if given IV → neurotoxicity → tremor of the lips and limbs, delirium, fits, stimulation followed by depression of respiration & coma **C.I.:** • Prolonged QT Interval, Glucose-6-Phosphate Dehydrogenase (G6PD) Deficiency, Myasthenia Gravis, Hypersensitivity, Optic Neuritis, auditory problems • Dose should be reduced in renal insufficiency **Drug interactions:** • Antacids containing aluminum &/or magnesium may delay or decrease absorption of Quinine, Mefloquine. • Quinine can raise plasma levels of warfarin and digoxin
Primaquine	Not well understood. It may be acting by: • Generating ROS → can damage lipids proteins & nucleic acids • Interfering with the electron transport in the parasite →no energy • Inhibiting formation of transport vesicles → no food vacuoles • Resistance: Rare when Primaquine & Chloroquine are combined	• Radical cure of relapsing malaria • In falciparum malaria	**At regular doses** patients with G-6-PD deficiency → hemolytic anemia. Oxidation of Primaqune produces free radicals, free radicals will cause oxidative damage of RBCs → Hemolysis **At larger doses:** • Epigastric distress & abdominal cramps • Mild anemia, cyanosis & methemoglobinemia	• Severe methemoglobinemia → rarely in patients with deficiency of NADH methemoglobin reductase. • Granulocytopenia & agranulocytosis (rare) **Notes:** • metabolized to etaquine & tafenoquine • Should be avoided in pregnancy (fetus is G6PD-deficient and at risk of hemolysis) • G6PD deficiency patients