MED438

pharmacology

Team 438

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Summary

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Lecture(1): H2 blockers and proton pump inhibitors

Drugs	MOA	Uses	ADRs	Precaution
Gastric hyposecretory drugs				
Proton pump inhibitors (MOST potent & Have H.Pylori INHIBITORY effect)				
Omeprazole **Lansoprazole** **Pantoprazole** **Raprazole**	**Irreversible inhibition of proton pump (H+/K+ ATPase)**	**- Eradication of H. pylori w/ antibiotics** **- Zollinger Ellison syndrome and gastrinoma (first choice)** - Resistant **severe** peptic ulcer - GERD	Short term use is safe but long may lead to: **-Achlorhydria & Hypergastrinemia** -Gastric mucosal hyperplasia -Infection Long term use: -Vitamin B12 deficiency -Hypomagnesemia -Osteoporosis - ↓iron absorption	Omeprazole should (CYT2c19 inhibitor) not be combined with clopidogrel (antiplatelet)
H2 receptor blockers				
Cimetidine Most toxic **Ranitidine** **Famotidine** Most Potent **Nizatidine** High Bioavailability	**- Reversibly and competitively block H2 receptors on parietal cells** **- Block nocturnal acid secretion** (which depends on histamine)	- GERD - Acute ulcer healing in **moderate** cases: - Duodenal ulcer - Benign gastric ulcer - Prevention of bleeding from stress-related gastritis - Pre-anesthetic medication - Post-ulcer healing maintenance therapy	**- Headache, confusion** (in elderly, hepatic\renal dysfunction) **- Bradycardia & hypotension** **Only cimetidine:** - CYT-P450 inhibition (↓Warfarin, phenytoin, Benzodiazepine) - Galactorrhea (hyperprolactinemia) - Antiandrogenic actions (gynecomastia -impotence)	- Severe renal\ hepatic failure and elderly
Mucosal cytoprotective agents				
Prostaglandin analogues (PGE1)				
Misoprostol	- ↓HCL production - ↑ protective measures (↑mucous/bicarbonate & gastric mucosal blood flow)	**Drug of choice for NSAIDs-induced peptic ulcer**	- Abdominal cramps, diarrhea - Uterine contraction (dysmenorrhea or abortion) - Vaginal bleeding	___

Lecture(1): H2 blockers and proton pump inhibitors

Drugs	MOA	Uses	ADRs
Neutralizing agents			
Antacids (Inorganic salts)			
Sodium bicarbonate [NaHCO3]	**Direct chemical neutralization** of HCL + decrease pepsin activity	**Relieve pain** of peptic ulcer & dyspepsia	- Systemic alkalosis **- C.I=CVS patent**
Aluminum hydroxxide [Al(OH)3]			**- Constipation** -Hypophosphatemia - Seizure
Magnesium hydroxide [Mg(OH)2]			**- Diarrhea** - Hypotension & cardiac arrest
Calcium carbonate [CaCO3]			**- Milk-alkali syndrome** - Hypercalcemia - Renal failure - Decreases absorption of tetracycline

Lecture(2): Antiemetic Drugs

Drugs	MOA	Uses	ADRs
Serotonin (5-HT3) antagonists (MOST POTENT antiemtics)			
Ondansetron **Granisetron**	blocking 5-HT3 receptor: **-Centrally** (in vomiting center, CTZ) **-Peripherally** (5HT3 receptors on GI vagal afferents)	**First choice** for prevention of moderate to severe emesis: -Chemotherapy-induced NV especially **cisplatin** (a strong emetogenic anticancer) -Post-radiation & Post-operative NV -Their effects are augmented by **combination** with corticosteroids and NK1 antagonists	-Headache -dizziness -constipation -Minor ECG abnormalities (QT prolongation)
D2 receptor antagonists			
Prokinetic D2 receptor antagonists			
Domperidone Doesn't cross BBB	**-Antiemetic action** by blocking D2 receptors in the **CTZ** **-Prokinetic action** by **5HT4 agonist** activity : **Increases upper GI motility and gastric emptying**	**For their antiemetic action:** -Vomiting due to: cytotoxic drugs, gastroenteritis, surgery, toxins, uremia, radiation **For their Prokinetic action:** -GERD -Gastroparesis	___
Metoclopramide cross BBB			-Dyskinesia -Galactorrhea -menstrual disorders -impotence -Postural hypotension -Sedation -drowsiness
Neuroleptics (Antipsychotics) D2 receptor antagonists			
Chlorpromazine (CPZ) **Droperidol**	**-Antiemetic action** by blocking D2 receptors in the **CTZ**	**-Postoperative vomiting** -Chemotherapy-induced NV	-Extrapyramidal symptoms -Sedation -Postural hypotension
Neurokinin-1 (NK1) receptor antagonists			
Aprepitant	Acts centrally as **substance P antagonist** by **blocking neurokinin-1 receptors** in vagal afferent fibers	Usually **combined** with 5-HT3 antagonists and corticosteroids in **prevention** of: -Chemotherapy-induced NV -Post-operative NV	___
Glucocorticoids			
Dexamethasone **Methyl-prednisolone**	___	**-Combined** with 5-HT3 antagonists or NK1 receptor antagonist. -used in chemotherapy induced NV	-Hypertension -Hyperglycemia -Cataract -Osteoporosis -Increased IOP -Increased susceptibility to infection -Increased appetite & obesity

Lecture(2): Antiemetic Drugs

Drugs	MOA	Uses	ADRs
H1-receptor agonists			
Diphenhydramine Promethazine Meclizine Cyclizine	___	-Motion sickness **-Morning sickness in pregnancy (Promethazine in severe cases)**	-Prominent sedation -Hypotension -Atropine like actions: ○dry mouth ○dilated pupils ○urinary retention ○constipation
Muscarinic receptor antagonists			
Hyoscine (Scopolamine)	Reduces impulses from vestibular apparatus	-As transdermal patches in **motion sickness** **-NOT USED IN chemotherapy-induced nv**	-Sedation -Atropine like actions: ○ Blurred vision ○ Tachycardia ○ Dry mouth ○ Constipation ○ Urinary retention

The choice of antiemetic depends on the etiology:

Motion sickness:

-Muscarinic antagonists
-Antihistamines

morning sickness:

- Avoid all drugs in the first trimester
- Pyridoxine (B6)
- Promethazine (late pregnancy)

Vomiting due to cytotoxic drugs:

- 5-HT3 antagonists
- NK1 antagonists
- D2- antagonists
- Glucocorticoids

Post operative NV

- Dopamine antagonists

NV due to infection

-Ondansetron (1st choice)
- Diphenhydramine
-Chlorpromazine

Drug- induced vomiting (CTZ), uremia, gastritis:

- Dopamine antagonists

Severe NV

-Glucocorticoids
-Serotonin (5-HT3) antagonists

NV due to migraine

-Diphenhydramine

Lecture(3): Therapy in IBD

Drugs	MOA	Uses	Site of Delivery\ADRs
Aminosalicylates (5-ASA)			
Azo Compound & Mesalamine The major differences are in **mechanism** and **site** of delivery			
Azo Compound: **-Sulfasalazine** **(5-ASA + sulphapyridine)** **-Olsalazine** **(5-ASA + 5-ASA)** **-Balsalazide** **(5-ASA + inert carrier)**	Have **TOPICAL** anti-inflammatory action due to: -inhibition of prostaglandins and leukotrienes. -decrease neutrophil chemotaxis -Antioxidant activity. -Different formulations (Azo component & Mesalamines) are used to **overcome rapid absorption** of 5-ASA from the proximal small intestine - All aminosalicylates are used for **induction and maintenance** of remission	-Induction and maintenance of remission in **mild to moderate** IBD **(First line of treatment)** **-Rectal** formulations are used in distal UC, ulcerative proctitis and proctosigmoiditis.	**Site of Delivery:** -azo bond is cleaved by **azoreductase** enzyme produced by bacterial flora **releasing 5-ASA in the terminal ileum and colon**
Mesalamines : **Oral:** **-Asacol** **-Pentasa** **Rectal:** **-Canasa** **-Rowasa**			**Site of Delivery:** **terminal small bowel & large colon** **Oral formulation:** starts at the pylorus and continues throughout the small bowel and colon. **Rectal formulation:** In the distal colon _____ **Features:** - Well tolerated -Sulfate free - useful in patient sensitive to sulfa drugs - Less ADRs
Azo Compound:			
Sulfasalazine (Azulfidine)	-In the terminal ileum and colon, sulfasalazine is broken by azoreductase Into: ○ 5-ASA (not absorbed, active moiety, **acting locally**) ○ Sulphapyridine (absorbed, **causes most of side effects**)	Another use: -Rheumatoid arthritis	**ADRs:** **-Due to Sulfapyridine:** 1-Folic acid deficiency (should be provided). 2.oligospermia 3. Megaloblastic anemia. 4.Crystalluria. 5.Bone marrow depression **-Due to 5-ASA:** 1. Interstitial nephritis

Lecture(3): Therapy in IBD

Drugs	MOA	Uses	ADRs
Glucocorticoids			
Prednisone **Prednisolone** (Orally)	-Inhibits phospholipase A2 -Inhibits gene transcription of NO synthase cyclooxygenase-2 (COX-2) -Inhibit production of inflammatory cytokines	**-ACUTE flares** of disease (**moderate to severe active IBD**) - Are **NOT** useful in **maintaining** remission **-Oral glucocorticoids:** used in active condition. -**Rectal glucocorticoids:** are preferred in **IBD** involving rectum or sigmoid colon. Other uses: -Asthma -Rheumatoid arthritis -immunosuppressive drug for organ transplants -Antiemetic during cancer chemotherapy	-More adverse effects compared to rectal
Hydrocortisone **Methylprednisolone** (Parenteral)			
Hydrocortisone (Rectal)			-Minimal side effects and maximum tissue effects
Budesonide	-A potent synthetic **prednisolone** analog	- Used in treatment of **active mild to moderate crohn's disease** involving **Ileum** and **Proximal colon**	-
Immunomodulators			
Methotrexate	**- a folic acid antagonist** -Inhibits dihydrofolate reductase required for folic acid activation (tetrahydrofolate) -Impairs DNA synthesis	- **Induce** **and** **maintain** remission in **IBD** in active **moderate to severe** conditions or steroid dependent or steroid resistant patients. Other uses: -Rheumatoid arthritis -Cancer	-Megaloblastic anemia -Bone marrow depression -Teratogenic
Purine analogs: **-Azathioprine** **-6-mercaptopurine**	- Inhibit purine synthesis and inhibits synthesis of DNA, RNA, and proteins. - It may decrease proliferation of immune cells, which lowers autoimmune activity.	- **Induce** **and** **maintain** remission in **IBD** in active **moderate to severe** conditions or steroid dependent or steroid resistant patients.	**- Bone marrow depression:** leucopenia, thrombocytopenia. **-Hepatic dysfunction** (CBC & liver function tests are required) -Gastrointestinal toxicity.

Lecture(3): Therapy in IBD

Drugs	MOA	Uses	ADRs
TNF-α inhibitors			
Adalimumab (Humira) (Fully humanized IgG)	- Act by binding to TNF-a thus preventing its binding to cell surface receptors. -↑ apoptosis of T-lymphocytes and monocytes.	-**moderate to severe** Crohn's disease -rheumatoid arthritis -psoriasis	-
Certolizumab (Cimzia) (Fab fragment of a humanized antibody)		- Crohn's disease -Rheumatoid arthritis	-
Infliximab (chimeric mouse-human monoclonal antibody) (2 weeks to give clinical response)		-**moderate to severe** active Crohn's disease and UC. - Patients **NOT** responding to immunomodulators or glucocorticoids. -rheumatoid arthritis. -Psoriasis.	- Acute or **early** infusion ADRs (Type 1 allergic reaction) - **Delayed** type hypersensitivity reaction (**serum sickness-reaction)** (**Pre-treatment** with diphenhydramine, acetaminophen, corticosteroids). **-Loss of response to infliximab** over time due to the development of antibodies to infliximab. -↑risk of opportunistic infection -Severe hepatic failure. -Rare risk of lymphoma

Lecture(4): Constipation and IBS

Drugs\Types	MOA	Uses	ADRs	C.I
Bulk Forming Laxatives				
Dietary fibers: **- Indigestible** parts of vegetables & fruits - Bran powder **Hydrophilic colloids:** - Psyllium seed - Methyl cellulose - Carboxymethyl cellulose (CMC) **Synthetic fibers:** -Polycarbophil	Dietary fibers and hydrophilic colloids **are non absorbable substances** → ↑ the bulk of intestinal contents **by water retention** → ↑ mechanical pressure on the walls of intestine (distend the colon) → **stimulation** of stretch receptors → ↑ peristalsis → evacuation of soft stool	-	**- Delayed** onset of action (1-3 days). - Intestinal obstruction **(should be taken with enough water)** - Bloating, flatulence, distension - Interfere with other drug absorption e.g. iron, cardiac glycosides.	**- not used for patients in which water intake is restricted like heart failure, Kidney failure.**
Osmotic Laxatives				
1.Sugars **Lactulose** (metabolized by bacteria to fructose and galactose that fermented into **lactic acid & acetic acid** that function as osmotic laxatives)	they remain in the bowel, attract and retain water by **osmosis** thereby increasing the volume of feces → ↑ peristalsis	-Prevention of **chronic constipation** - Hemorrhoids - Hepatic encephalopathy (Hyperammonemia) **-Liver cirrhosis** (trapping NH_3 in the colon by forming non absorbable NH_4)	**- Delayed** onset action (2-3 Days) **- Electrolyte disturbance.** - Abdominal cramps & flatulence.	-
2.Saline laxatives **Have rapid effect** **- Magnesium sulphate/Citrate (Epson's salt)** **- Magnesium hydroxide(milk of magnesia)**		-Treatment of **acute and chronic constipation (Magnesium hydroxide)** - Treatment of **acute constipation, cleanse of bowl (Magnesium sulphate/Citrate)** **Has antacid effect (Magnesium hydroxide)**	**-Disturbance of fluid and electrolyte balance** -Dehydration -**Sodium phosphate:** -May causes low K or high Na, PO3 **-Cardiac arrhythmias** -Acute renal failure "**nephrocalcinosis**"	**- Renal failure** **Hypermagnesemia** **- Heart block** **-CNS depression** **-Neuromuscular block**
- Sodium phosphate **- potassium phosphate.**				**congestive heart failure**
3. PEG **Balanced Polyethylene Glycol (PEG)** (a colonic lavage solution)		**- Used for whole bowel irrigation prior to colonoscopy or surgery**	**Advantages:** - Limited fluid or electrolyte imbalance - less flatulence and cramps	-

Lecture(4): Constipation and IBS

Drugs	MOA	Uses	ADRs
Stimulant Laxatives (Most Powerful Group, Should be used carefully)			
Anthraquinone derivatives - Senna - Cascara - Aloe vera **(Active by-product: Anthranol)**	- Act via **direct stimulation** of enteric nervous system→ increased peristalsis & purgation.	- In patients who are **neurologically impaired** - in bed- bound patients in long term care facility **Castor oil**: Could be employed after oral ingestion of a toxin	**- Prolonged use** → **dependence** & destruction of myenteric plexus leading to **atonic colon.** **Anthraquinone derivatives:** Prolonged use→ brown pigmentation of the colon **"Melanosis coli"** **C.I of Castor oil**: **pregnancy** → reflex contraction of uterus → abortion.
Diphenyl methane derivatives - Bisacodyl **(Active by-product: Diphenyl Methane)**			
Castor oil **(Active by-product: Ricinoleic acid)**			
Serotonin 5HT4-receptor agonists			
Prucalopride	- Stimulation of 5HT4 receptors with enterokinetic activities	- used for **chronic constipation** in women	**- Advantage**: Lack CVS side effects
Fecal Softeners (Lubricants)/surfactants			
Docusate **(↓ surface tension)**	- Act by either ↓ **surface tension** allowing water to interact with the stool or by **softening the feces** thus promoting defecation. - used Treat constipation in patients with hard stool or specific conditions and for people who should avoid straining	**Used In hospitalized patients to↓constipation & straining.**	-
Glycerin **(Softening the feces)**		**Preferable in children**	
Paraffin oil **(Softening the feces)**		**Good for radiology preparation** **-** prevent fecal impaction in children & debilitating adults	Impairs absorption of fat soluble vitamins
Chloride secretion activators			
Lubiprostone	It stimulates type 2 chloride in the small intestine→↑Cl –fluid rich fluid→ intestinal motility	used for **chronic constipation** & IBS-C	After discontinuation, constipation may return to pretreatment
Linaclotide	stimulates chloride secretion		Most common ADR is diarrhea

Lecture(4): Constipation and IBS

Drugs	MOA	Uses	ADRs
Opioid receptor antagonists			
Methylnaltrexone	μ- receptor antagonist	**is used in opioid-induced constipation** in patients receiving palliative care for advanced illness.	-
Alivimopan		**used for short term to shorten the period for postoperative ileus**	
Irritable bowel syndrome (IBS)			
Symptomatic treatment of IBS			
Alosetron	Selective 5HT3 **antagonist** of the enteric nervous system of the gastrointestinal tract results into: -inhibition of colon motility. -inhibition of unpleasant visceral afferent pain sensation	**- Use restricted in IBS with severe diarrhea** in women who have not had success with any other treatment.	-Severe constipation and **ischemic colitis** may occur (People taking alosetron must sign a consent form before starting to take the medicine)
Tegaserod	- 5HT4 **agonist** of enteric nervous system of GIT → increases peristalsis.	- Short term treatment of **IBS-associated with constipation** with **no history of heart problems** - limited for **emergency situations.**	**-CVS side effects**

Lecture(5): Treatment of Dysentery and Amoebiasis

Drugs	MOA	Uses	ADRs	C.I
Antidiarrheal Drugs				
Loperamide (Doesn't cross BBB) (μ-opioid receptors **in the myenteric plexus** of the colon)	opioid-receptor agonist (Reducing GI motility)	-	-minimal liability for addiction	1. high fever 2. bloody stool. 3. C. difficile infections (b\c they delay fecal excretion-> prolong fever-> toxin retention -> toxic megacolon).
Diphenoxylate + Atropine (cross BBB)			-higher liability for addiction -atropine ADRs	
Antiamebic drugs				
Tissue or Systemic Amebicides (For Invasive Amebiasis, Should be followed by luminal amebicides)				
Metronidazole	Aon **trophozoites** by: **- Inhibiting DNA replication**	**-Drug of Choice** for treating invasive amebic infections (intestinal & extraintestinal amebiasis) Others: -Giardiasis -Trichomoniasis -Anaerobic bacterial infections: -Peptic ulcer(H.pylori). -Pseudomembranous colitis (C.difficile).	**GIT:** -Dry mouth, metallic taste. -N&V, diarrhea. -Oral Thrush (Moniliasis, yeast infection). **CNS: Neurotoxic** -Insomnia, dizziness -Peripheral neuropathy, paresthesia. -Encephalopathy, convulsion(rare) **Others:** -**Dysuria**, dark urine & **neutropenia** -**Disulfiram-like effect** if taken with alcohol.	-CNS diseases -Alcohol intake **-Pregnancy and breastfeeding women** **-Severe renal disease** **-Severe hepatic disease**
Tinidazole	similar activity to metronidazole but better potency	**Advantages of tinidazole :** ○ has **longer** duration of action (12-14h) ○ a **simpler** dosing regimen ○ a **better** toxicity profile than metronidazole.		
-Emetine **-Dehydroemetine** (less toxic than Emetine)	Both are **effective against tissue trophozoites** of E. histolytica causing irreversible block of protein synthesis.	**-Severe** forms of amebiasis **acute amoebic dysentery** (**dehydroemetine** is preferable due to less toxicity) -Amoebic liver abscess -Intestinal wall infections	**-Serious toxicity: cardiotoxicity** (Hypotension, cardiac arrhythmias, heart failure), **thus they have been completely replaced by metronidazole** -GIT: nausea, vomiting, diarrhea	- Patients with cardiac or renal disease - Young children - Pregnancy
Chloroquine	Anti-malarial drug	-combination w\ metronidazole or dehydroemetine **for amebic liver diseases.**	-Pruritus(common) **- Blurring of vision** **-Hemolysis in G6PD deficient patients**	-

Lecture(5): Treatment of Dysentery and Amoebiasis

Drugs	MOA	Uses	ADRs	C.I
Antiamebic drugs				
Luminal Amebicides (For Asymptomatic\carriers)				
Diloxanide furoate (unabsorbed diloxanide is the amoebicidal agent)	**-Unknown MOA** **-Direct** amoebicidal action against luminal forms (**Cyst**)	**Drug of choice** for asymptomatic intestinal infection -To eradicate cysts of E.histolytica after treatment of invasive disease with systemic amebicides	-Flatulence -Nausea, vomiting, abdominal cramps.	-Pregnancy -Children (< 2 years).
Iodoquinol	**-Unknown MOA** -Effective against the **luminal forms** of amebiasis	Luminal amoebicide for asymptomatic amebiasis	**GIT:**N&V, diarrhea. **-Peripheral neuropathy including optic neuritis** **-Enlargement of the thyroid gland** -Iodine sensitivity -interference with thyroid function tests	**-with caution in pt w/ optic neuropathy, or thyroid disease** -discontinued if it produces persistent diarrhea or signs of iodine toxicity (dermatitis, urticaria, pruritus, fever)
Paromo-mycin sulphate	-Aminoglycoside antibiotic **-Direct amebicidal action:** causes leakage by its action on cell membrane of parasite **-Indirect effect:** killing of bacterial flora essential for proliferation of pathogenic amoebae	Use in **chronic amebiasis** to eliminate cysts (in cysts passers)	Gastrointestinal distress and diarrhea	-Severe renal disease -Patients with GIT ulceration
Bacillary dysentery				
Ciprofloxacin (Gram +ve & -ve) **1st line**	Block bacterial DNA synthesis and growth (DNA gyrase and topoisomerase)	**Drug of Choice** for bacillary dysentery -Fluoroquinolones are **first-line** treatment for shigellosis **-Bacterial diarrhea** caused by shigella, salmonella and E. coli	-Arthropathy (damage of growing cartilage) -Phototoxicity -Liver toxicity -GIT disorder (N&V, diarrhea) - CNS disorders (headache, dizziness) **-CVS disorders** (prolong QT interval)	-Children, pregnancy, nursing mother. -Epilepsy -Should not be combined with antacids, divalent cations -Arrhythmias
Cephalosporin 3rd gen: -Cefixime, -Ceftriaxone **2nd line**	Act by inhibiting cell wall synthesis interfering with synthesis of peptidoglycan	**Drug of Choice** in case of pregnancy or children -In case of children or patient **allergic** to sulfonamides, cephalosporins or azithromycin may be used.	___	___

Lecture(6): Hepatotoxic Drugs

Types of drug-induced hepatotoxic

Intrinsic hepatotoxin

Causes Direct hepatotoxicity.

- Inflicted by:
  1. Super-therapeutic (increased) dose
  2. Cumulative dose [1]
- belong to **type A** ADRS :
  - **predictable** /direct.
  - **Dose-dependent** hepatotoxicity

Idiosyncratic hepatotoxin

Causes Indirect hepatotoxicity

- Inflicted by: Normal dose.
- Belong to **type B** ADRS:
  - **bizarre / unpredictable / idiosyncratic** .
  - **Dose-Independent** hepatotoxicity.

Drugs that are Intrinsic hepatotoxin

Increased Dose	Cumulative Dose	Both
• Acetaminophen • Salicylates • Statins	• Amiodarone • Oral contraceptive	• Methotrexate • Alcohol

Drugs that are Idiosyncratic hepatotoxin

Divided into:

Immunologic-idiosyncratic Hepatotoxicity		Metabolic-idiosyncratic Hepatotoxicity	
Inflammatory cholestasis	Viral hepatitis-like pattern	Interfere with bilirubin metabolism	Interfere with protein synthesis
• Erythromycin • Chlorpropamide • Chlorpromazine	• Isoniazid • Phenytoin • Methyldopa	• Erythromycin • Rifampicin	• Corticosteroid • Tetracycline

Clinical Patterns of Drugs induced hepatotoxicity

Injury	Hepatocellular	Cholestatic	Mixed
How They Develop	If injury targets hepatocytes → apoptosis or necrosis → HEPATITIS develops → rapid onset of malaise, severe anorexia and jaundice + ↑ in alanine aminotransferases (ALT)	If injury targets biliary system →CHOLESTASIS develop → jaundice +\- severe pruritus predominate → ↑ in alkaline phosphatase (ALP) +\- hyperbilirubinemia.	if injury targets both hepatocytes & biliary system→ MIXED TYPE.
Symptoms	Flu-like, malaise, muscle aches weakness, loss of appetite, GIT symptoms, diarrhea, jaundice, urine discolored.	Yellowish discoloration of skin, dark urine, rash, pruritus, stool may be light	Symptoms of both types of injury (Hepatocellular and Cholestatic) are present
↑Enzyme	ALT Only	ALP only	Both increase
E.g	1. Acetaminophen 2. NSAIDs 3. Isoniazid 4. Amiodarone	1. Chlorpropamide 2. Erythromycin 3. Rifamycin 4. Oral contraceptives	1. Phenytoin 2. Carbamazepine 3. Sulfonamides 4. ACE Inhibitors

Treatment

Nonspecific treatment:
- **Corticosteroids** for severe allergic reactions
- **Cholestyramine** for pruritus
- **ursodeoxycholic acid (Ursodiol)** for cholestatic liver injury

Specific antidotes:
- **N-acetylcysteine** for acetaminophen toxicity
- **L-carnitine** for valproate toxicity

Lecture(7): CYT P450

Substrate	Inducers	Inhibitors
CYT P450 3A4		

• Ca^{+2} channel blocker
  ○ Amlodipine
  ○ Verapamil
• Benzodiazepines
  ○ Midazolam
  ○ Clonazepam
• HMG-CoA- reductase inhibitors (statins)
  ○ Atorvastatin
• Immunosuppressants
  ○ Cyclosporine
• Azole Antifungals
  ○ Fluconazole
• Antibiotics
  ○ Erythromycin
  ○ Clarithromycin
• Cancer Chemotherapy
  ○ Cyclophosphamide
  ○ Tamoxifen
• Non-Sedating Antihistamines
  ○ Astemizole
	• Rifampicin
	• Phenytoin
	• Carbamazepine
	• Barbiturates
	• Dexamethasone
	• Progestins
	• Rifabutin
		• Grapefruits
		• Nefazodone
		• H2 Blocker
		  ○ Cimetidine
		• Immunosuppressant
		  ○ Cyclosporine
		• Azole Antifungals
		  ○ Fluconazole
		  ○ Ketoconazole
		  ○ Itraconazole
		• Antibiotics
		  ○ Erythromycin
		  ○ Clarithromycin
		  ○ Troleandomycin
		  ○ Chloramphenicol
		• Protease Inhibitors
		  ○ Ritonavir

CYT P450 2D6		

• Codeine
• Many B-blockers
  ○ Propranolol
  ○ Metoprolol
  ○ Timolol
  ○ Bupranolol
• Many tricyclic antidepressants
	• Rifampicin	• Fluoxetine
		• Haloperidol
		• Paroxetine
		• Quinidine

Genetic variation of 2D6

the most frequent polymorphisms → ↓ metabolizing capacity

➔ 1-Metabolism of some drugs **are suppressed** , so side effects & **toxicity** develop. i.e.:

- Neuropathy after therapeutic doses of perhexiline
- Bradycardias & arrhythmias on therapeutic dose of propafenone or metoprolol

➔ 2-The **pro-drugs** **cannot be converted to their therapeutically active metabolite**
e.g. poor analgesia with codeine & tramadol because they are not transformed into active forms.

CYT P450 1A4		
• Theophylline • Imipramine • Propranolol • Clozapine	• smoking tobacco	• Many fluoroquinolone antibiotics • Fluvoxamine • Cimetidine

Lecture(7): CYT P450

Substrate	Inducers	Inhibitors
CYT P450 2C9		

• Most NSAIDs (including COX-2)
  ○ Celecoxib
  ○ Diclofenac
  ○ Ibuprofen
  ○ Tolbutamide
• S-warfarin (the active form)
• Phenytoin
	• Rifampicin
	• Barbiturates
		• Fluconazole

Genetic variation of 2C9		
• Warfarin, phenytoin, & tolbutamide are examples of drugs with **narrow therapeutic index** that are metabolized by CYP2C9 • Clearance of these drugs **is impaired** in genetic variation of the enzyme		
CYT P450 2C19		
• Diazepam • Omeprazol • Phenytoin	• Rifampicin • Barbiturates	• Omeprazole • Isoniazid • Ketoconazole
Genetic variation of 2C19		
• Polymorphism in CYP2C19 shows increased & prolonged action of its substrates as omeprazole. • This has been an **advantage as in those variants there is↑ cure rates in peptic ulcer** patient with Helicobacter pylori **(beneficial effect)** .		

Lecture(8): Anticoagulants

Uses of Anticoagulant

1. Myocardial infarction (MI)
2. Deep venous thrombosis (DVT)
3. Peripheral arterial emboli, pulmonary embolism (PE) and many other conditions
4. Blood transfusions and dialysis procedures

Drugs	MOA	Uses	ADRs	C.I
Parenteral Anticoagulant				
Indirect Thrombin Inhibitors (Unfractionated heparin "UFH")				
Unfractionated heparin Rapidly acting Monitoring method: activated partial thromboplastin time (aPTT) Not injected IM	- It acts indirectly by **increasing the activity** of the **"antithrombin III"** (1000 folds) which **inhibits activated clotting factors mainly thrombin (factor IIa) and Xa.**	**-Drug of choice** for pregnancy b\c it **doesn't cross the placenta.** - Rapid anticoagulation (intensive) ———— **ANTIDOT: protamine sulfate**	- The major adverse is **bleeding** - **osteoporosis** in long term use **- Heparin-induced thrombocytopenia (HIT)** - Allergic reactions	- Bleeding disorders, hemophilia -Patients with hypersensitivity to the drug -Recent surgery of the brain, eye or spinal cord, threatened abortion
Indirect Thrombin Inhibitors (Low-Molecular-Weight Heparins "LMWHs")				
Heparin fragments: **- enoxaparin** **- dalteparin**	**increase the action of antithrombin III on factor Xa (ONLY)**	-Used increasingly in place of unfractionated heparin.	-	-
Synthetic pentasaccharide: **-fondaparinux** less likely than UFH or LMWH to trigger HIT				

★ Differences between UFH and LMWH

- **UFH:**
  - No predictable anticoagulant effects
  - Low bioavailability
  - Need for regular monitoring (aPTT)
  - Heparin-induced thrombocytopenia (HIT)
  - Used in hospital only
  - Complete response to the antidot
- **LMWH:**
  - More predictable effect
  - Good bioavailability
  - No need for laboratory monitoring
  - ↓Incidence of thrombocytopenia
  - Used in hospital and outpatient clinic
  - Incomplete response to the antidot

Direct Thrombin Inhibitors				
Hirudin **Lepirudin**	Exert their effect by **direct binding to thrombin.** **(rapid & potent)**	-	**ADVANTAGE: Are not associated with thrombocytopenia.**	(Females' slides) -

Lecture(8): Anticoagulants

Drugs	MOA	Uses	ADRs	C.I
Oral Anticoagulants				
Vit K Antagonist				
Warfarin (Coumarin) **98% bound to plasma proteins** **Monitoring method: Prothrombin time (PT) ; International Normalized Ratio (INR)**	- **Inhibits synthesis of Vitamin K-dependent coagulation factors** II, VII, IX, & X as well as anticoagulant proteins C & S by the action of **Vit K epoxide reductase antagonism** **- Has delayed onset b\c it doesn't have an effect on already-synthesized coagulation factors**	-Long term anticoagulation (Controlled) _____ **ANTIDOT:** -Stop the drug -IV injection of vitamin K to ↑Vit k cofactor synthesis (slow onset) -Fresh frozen blood (Fast onset)	**- Bleeding** _____ **DISADVANTAGES:** **-** Unpredictable effect thus **necessitating regular INR monitoring** - **Narrow therapeutic window** **-** Slow onset and offset of action, so **not in given in emergency conditions** **-**Numerous food- & drug-drug interactions	**- pregnancy** as it **can cross the placental barrier** and cause abortion, hemorrhagic disorder in the fetus and birth defects

Differences between Heparin and Warfarin

- **Heparin:**

- **MOA:** ↑ Activity of Antithrombin III
- Given parenterally (IV,SC)
- Does not cross placenta
- **Monitoring:** aPTT
- **Antidot:** Protamine sulfate
-Used in rapid anticoagulation (intensive)
-**Toxicity:** Bleeding, Osteoporosis, HIT, Hypersensitivity

- **Warfarin:**

- **MOA:** ↓Hepatic synthesis of vit k- dependent factors
- Given orally
- Cross placenta
- **Monitoring:** PT; INR
- **Antidot:** ↑Vit k cofactor synthesis (slow onset), Fresh frozen plasma (fast onset)
-Used in long term anticoagulation (controlled)
-**Toxicity**: Bleeding, Skin necrosis (if low protein C), Drug interactions, Teratogenic

Lecture(9): Antiplatelet Drugs

Drugs	MOA	Uses	ADRs
Arachidonic acid pathway inhibitors			
Aspirin	**- Irreversible** inhibition of cyclooxygenase enzyme (**COX-1**) via acetylation,thus inhibiting synthesis of TXA2.	**- 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 **clopidogrel** or **heparin**.	- Risk of peptic ulcer. - Increased incidence of GIT bleeding -Hyperacidity **C.I=** Peptic ulcer
Adenosine Diphosphate (ADP) pathway inhibitors (Prodrugs)			
Ticlopidine **Clopidogrel** (replaced ticlopidine b\c: **less neutropenia**, more potent, longer duration, given once, bioavailability not affected by food)	- These drugs specifically and **irreversibly inhibit ADP receptor P2Y12**, which is required for platelets activation thus prevent platelet aggregation.	**- Secondary prevention**[1] of ischemic complications after myocardial infarction, ischemic stroke and unstable angina. -**Given with aspirin** in high risk patients (Heart attack, severe attack of angina, coronary angioplasty, stenting). **Specific for clopidogrel:** - For patients with **acute coronary syndrome** either those managed medically or with coronary angioplasty with or without stent.	**- Severe neutropenia** (**Ticlopidine**), regular monitoring of WBC count during first three months - leucopenia - Bleeding - GIT: nausea, dyspepsia, diarrhea. - Allergic reactions. - thrombotic thrombocytopenic purpura
New ADP Pathway Inhibitors (have more rapid onset, Are not prodrugs)			
Prasugrel	**- Irreversible** inhibitor of the P2Y12 receptor	- to reduce the rate of thrombotic cardiovascular events (including stent thrombosis) in patients with acute coronary syndrome who are to be managed by PCI.	- both increase bleeding risk. - Ticagrelor causes dyspnea.
Ticagrelor	**- Reversible** inhibitor of the P2Y12 receptor		
Glycoprotein IIb/ IIIa receptor inhibitors			
Abciximab	**- GPIIb/IIIa receptor Receptor Blockers** (stop clot formation)	- used with **heparin and aspirin** as adjunct to PCI for the prevention of cardiac ischemic complications	- Bleeding and Thrombocytopenia
Tirofiban (non-peptide drug) **Eptifibatide** (peptide drug)		- Used for the reduction of incidence of thrombotic complications during coronary angioplasty (PCI) and acute coronary syndrome.	
Phosphodiesterase inhibitor (Vasodilators)			
Dipyridamole	**- Inhibits phosphodiesterase** thus increases cAMP and **decreased synthesis of thromboxane A2** .	- Adjunctive therapy for prophylaxis of thromboembolism in cardiac valve replacement (with warfarin). - Secondary prevention of stroke and transient ischemic attack (with aspirin).	-Headache -Postural hypotension
Cilostazol **(Better choice than dipyridamole in patients with coronary problems)**	**- Phosphodiesterase inhibitor (PDE3)**	**- Prevent intermittent claudication**	-

Lecture(10): Antimalaria

Drugs	MOA	Uses	ADRs	C.I\Resistance
Artemisinin **Derivatives:** **-Artesunate** **-Artemether** **(Acts on blood Schizonticide)**	-They have **endoperoxide bridges** that are cleaved by haem iron to yield carbon- centered free radicals in parasite, that will: -deplete its **energy** **-inhibiting its growth** **- inhibits food vacuoles formation**	-Affect all forms including multi-drug resistant P. falciparum -Monotherapy **should be extended** beyond disappearance of parasite to **prevent recrudescence** -By combining the drug with long acting antimalarial drug e.g:Mefloquine -Artesunate IV or IM preparations **for severe complicated cases as cerebral malaria (24h)** followed by complete course of ACT.	-Transient heart block. -Decrease neutrophil count -Brief episodes of fever -Resistance -High recrudescence rate	**Preparation:** Artemisinin based Combination Therapies (ACTs): - Artemether + lumefantrine - Artemether + amodiaquine - Artemether + mefloquine - Artemether + (sulfadoxine - pyrimethamine)
Chloroquine **(Potent blood Schizonticide)** **(Highly bound to tissue)**	- Malaria Parasite digest host cell's Hb to utilize globin & obtain amino acids. - Heme is released → **Toxic for the parasite**, so parasite detoxifies it by **heme polymerase**→ Hemozoin (NonToxic) & traps it in food vacuoles **-Chloroquine\quinine prevents the polymerization of heme to hemozoin by inhibiting Heme Polymerase enzyme**	-Against all species except P. falciparum - Used to eradicate **blood** schizonts of Plasmodium. -Hepatic amebiasis -Rheumatoid arthritis. **-Safe in pregnancy**	-Mild headache & visual disturbances - Pruritus, urticaria. **Prolonged therapy & high doses:** -Ocular toxicity (Loss of accommodation, lenticular opacity, retinopathy) -Ototoxicity -Weight loss -Bolus injection → hypotension & dysrhythmias	**Resistance:** -mutation of the chloroquine resistance transporter (PfCRT)
Quinine **(Potent blood Schizonticide)** **(Have curare mimetic effect)**		-Parenteral treatment of **severe falciparum malaria** -Oral treatment of falciparum malaria -Nocturnal leg cramps **-Safe in pregnancy** (1st trimester)	**-Blackwater fever,** (fetal acute haemolytic anaemia is associated with renal failure due to a hypersensitivity reaction) -Higher doses: Cinchonism (tinnitus, deafness, headaches, nausea & visual disturbances) -Hypotension & arrhythmias, hypoglycemia -Blood dyscrasias (**anaemia**, thrombocytopenic purpura & hypoprothrombinemia) -If given IV it causes neurotoxicity →tremor of the lips & limbs, delirium, fits,stimulation followed by depression of respiration & coma	**C.I:** -Prolonged QT Interval -G6PD deficiency & pregnancy -Myasthenia Gravis -Hypersensitivity -Optic Neuritis, auditory problems -Dose should be reduced in renal insufficiency **Resistance:** -mutation of the chloroquine resistance transporter (PfCRT) **&** increased expression of P-glycoprotein transporter

Lecture(10): ANTI-MALARIA

Drugs	MOA	Uses	ADRs	C.I
Primaquine **(against liver hypnozoites)**	**- Generating ROS** → can damage lipids, proteins & nucleic acids in the parasite -Interfering with the electron transport in the parasite → no energy -Inhibiting formation of transport vesicles → no food vacuoles	-**against the 4 human malaria species** - Radical cure of relapsing malaria -Prevent spread of all forms (chemoprophylaxis)	**at regular doses:** -patients with G-6-PD deficiency → hemolytic anemia. -produces free radicals which cause oxidative damage of RBCs → Hemolysis **At larger doses:** -Epigastric distress & abdominal cramps -Mild anemia, cyanosis & methemoglobinemia -Granulocytopenia & agranulocytosis (rare)	**-pregnancy** **-G6PD deficiency.**

Drug Interactions

Drugs\Class	Interactions
Warfarin	• **Increase Warfarin activity** 1. Inhibition of Vit. K synthesis by intestinal flora; **oral antibiotics** 2. Inhibition of Vit K absorption; **liquid paraffin** 3. Decrease in drug metabolism by microsomal enzyme inhibitors; **chloramphenicol, & cimetidine** 4. Displacement of the drug from protein binding sites; **phenylbutazone & salicylates** 5. Co-administration of drugs that increase bleeding tendency by; a. Inhibiting platelet function; **NSAIDs** b. Inhibiting coagulation factors; **heparin** • **Decrease Warfarin activity** 1. Inhibition of drug absorption from GIT; **cholystyramine, colestipol** 2. Increase in synthesis of clotting factors; **Vit K, oral contraceptives** 3. Increase in drug metabolism by microsomal enzyme inducers; **Carbamazepine; barbiturates, rifampicin**
Metronidazol	• **Enzyme <u>inhibitors</u>** E.g. cimetidine, ketoconazole → **increase** duration of action of Metronidazole • **Enzyme <u>inducers</u>** E.g phenytoin, phenobarbitone → **decreased** duration of action of Metronidazole • **Metronidazole inhibits CYP-450 (2C9 & 3A4) so:** increases anticoagulant effect of **warfarin &** increases **lithium** toxicity • Combining metronidazole and alcohol **causes nausea, vomiting, abdominal distress, flushing, headache, tachycardia,hyperventilation** (disulfiram-like effect)
Quinine	• Antacids: Antacids containing aluminum &/or magnesium may delay or decrease absorption of quinine • Mefloquine • Quinine can raise plasma levels of warfarin & digoxin
Ticlopidine Clopidogrel	• inhibit CYT P450 causing increased plasma levels of drugs such as phenytoin and carbamazepine.