Ftplectures Pharmacology Lecture Notes

PHARMACOLOGY

Pharm made simple

Ftplectures Clinical Medicine
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The field of Medicine is an ever-changing profession and as new evidence based studies are conducted, new knowledge is discovered. Ftplectures has made tremendous effort to deliver accurate information as per standard teaching of medical information at the time of this publication. However, there are still possibilities of human error or changes in medical sciences contained herein. Therefore, ftplectures is not responsible for any inaccuracies or omissions noted in this publication. Readers are encouraged to confirm the information contained herein with other sources.

Adrenergic agonist

Adrenergic agonists are the drugs that use adrenaline. They bind with the adrenergic receptor alpha or beta.

Direct acting adrenergic agonists:

Alpha receptor agonists:

These agonists specifically act on the alpha receptors:

- Methyldopa.

Clonidine:

Clonidine is an alpha 2 receptor agonist. It decreases the norepinephrine by a negative feedback mechanism via receptors on the presynaptic neurons.

Clinical uses:

- Used to treat hypertension.
- Opioid withdrawal/benzodiazepine withdrawal.
- Used to treat diabetic autonomic neuropathy.

Adverse effects:

- Orthostatic hypotension.
- Sedation.
- Sexual dysfunction.
- Dry mouth.

Phenylephrine:

Phenylephrine specifically binds on the alpha 1 receptor. When it binds on the alpha 1 receptors then biochemical cascade begin. It activates the Gq protein and Gq protein activates the phospholipase C. it cleaves the lipid in the cell membrane and PIP2 and it further converted into diacylglycerol (DAG) which activates the protein kinase c and inositol phosphate (IP2) causes increases in the intracellular calcium (Ca2+) which is responsible for vasoconstriction.

Clinical uses:

- Phenylephrine is used to treat the hypotension because it causes increase in the blood pressure.
- Used as nasal decongestant.
- Used to treat mydriasis.

Adverse effects:

- Rebound mucosal swelling.
- Hypertensive headache.

Beta receptor agonists:

These agents specifically act on the beta receptors:

Dobutamine:

Dobutamine acts specifically beta1 receptors which are present on the heart and activates second messenger via Gs protein and this protein activates adenylcyclase. It activates ATP into cAMP and cAMP increases the intracellular calcium (Ca2+) and in turn contraction of the smooth muscle increases and in this way dobutamine increases the heart rate and contractility.

Clinical uses:

- Cardiogenic shock.
- Congestive heart failure (CHF).

Adverse effects:

- Arrhythmias.
- Headache.
- Palpitations.
- Hypertension.

Isoproterenol:

Isoproterenol acts specifically on both beta1 and beta2 receptors. When it binds to beta1 it increases the heart rate and contractility. When it binds to beta2 smooth relaxes and thus lowers the total peripheral resistance.

Clinical uses:

- Heart block/bradycardia.

Adverse effects:

- Arrhythmias
- Palpitation.

Albuterol/Metaproterenol/Terbutaline:

These drugs act on the beta2 receptors.

Clinical uses:

- Used to treat asthma.
- COPD.
- Bronchitis.

Ritodrine:

Ritodrine also acts on the beta2 receptors but it acts on uterus and decreases the contraction of the uterus.

Clinical uses:

- Prevent pre-mature labour.

Alpha/beta receptor agonists:

Epinephrine:

It acts on all the adrenergic receptors (alpha1&2, beta1&2).

Clinical uses:

- Anaphylaxis (type 1 hypersensitivity).
- Hypotension (shock)-septic shock.
- Open angle glaucoma.
- Asthma.

Nor-epinephrine:

Acts on alpha 1&2, Beta 1 and it decreases renal perfusion.

Dopamine:

Dopamine acts on alpha 1&2, beta1&2, dopamine receptors. In **low dose** it acts on dopamine receptors and increases renal perfusion, in **medium dose** it acts on beta receptors and starts acting like an inotrope, in **high dose** it acts on alpha receptor as a vasopressor.

Clinical uses:

- Hypotension.
- Heart failure.

Indirect adrenergic agonists:

- Ephedrine.
- Amphetamines.

Autonomic nervous system pharmacology

Human nervous is composed of two parts:

1. Central nervous system.
2. Peripheral nervous system.

Peripheral nervous system is further divided into:

1. Somatic nervous system
2. Autonomic nervous system.

Autonomic nervous is further divided into following:

- Sympathetic nervous system
- Parasympathetic nervous system.

Sympathetic nervous system:

Sympathetic nervous works whenever fight or flight is required it uses norepinephrine and epinephrine as a neurotransmitter it has following receptors:

- Alpha 1
- Alpha 2
- Beta 1
- Beta 2

Sympathetic system is lumbosacral system (T1-L5). Preganglionic nerves are very long and use acetylcholine and acetylcholine attaches to nicotinic (neuronal) receptors and stimulates the postganglionic receptors. Post ganglionic releases either epinephrine or nor-epinephrine. Dopamine also binds to D1 receptors on the kidneys and causes vasodilation of the renal system. Sweat gland is the exception of the sympathetic nervous system and acetylcholine is released by the post-ganglionic neurons in the sweat glands pathway.

Organ system effects:

Eyes:

Pupils dilated (mydriasis) when sympathetic system is stimulated.

Heart:

SA node and AV node is stimulated and causes increase in the heart the rate and increase contractility.

Lungs:
Cause bronchodilation in lungs.

Gastrointestinal tract:
cause decrease in gastrointestinal motility.

Blood vessels:
Cause vasoconstriction.

Genito-urinary system:
Help you to hold the urine by contraction of the sphincter. Sympathetic system causes contraction of the uterus. Sympathetic system causes ejaculation of the semen from penis.

Sweat glands:
Cause sweating when the person runs.

Adrenal glands:
Cause release of the epinephrine and nor-epinephrine.

Kidneys:
Sympathetic system causes release of renin, which in turns increases blood pressure.

Skeletal muscle:
Cause glycogenolysis and increases contractility of the skeletal muscle.

Pancreas:
Sympathetic system causes decreases in insulin secretion and causes lipolysis in fat cells.

Parasympathetic nervous system:
Parasympathetic nervous works whenever we relax and it uses acetylcholine as a primary neurotransmitter it has different receptors than sympathetic:

- Muscarinic receptors:
    1. M1 receptor.
    2. M2 receptor.
    3. M3 receptor.
    4. M4 receptor.
    5. M5 receptor.
- Nicotinic receptors:
    1. Nn (neuronal).
    2. Nm (neuromuscular).

Parasympathetic is cranio-sacral system and cranial nerves 3, 7, 9, 10 are parasympathetic nerves. Preganglionic nerves are very long and use acetylcholine and acetylcholine attaches to

nicotinic (neuronal) receptors and stimulates the postganglionic receptors. Post ganglionic neuron releases acetylcholine.

Organ system effects:

Eyes:
Circular muscles stimulate and cause constriction (miosis).

Heart:
Heart muscle relaxes and decreases in heart and contractility occurs.

Lungs:
Cause broncho-constriction in lungs.

Gastrointestinal tract:
Help in gastrointestinal motility.

Blood vessels:
Vasodilation occurs.

Genito-urinary system:
Cause urination by relaxing the sphincter and contracting the detrusor muscle. Parasympathetic relaxes the uterine muscle. Parasympathetic system causes erection of the penis.

Cholinergic antagonists

Atropine/homatropine/tropicamide:

Mechanism of action:

Anti-cholinergic drugs block the cholinergic receptors by binding with the receptors and block all the activity of G-proteins inside the cell that is responsible for the initiation of the cellular activity.

Clinical uses:

Atropine reversibly binds to the cholinergic receptors, clinically use for eyes to dilate the pupils (**mydriatics**). It also causes **cycloplegia** (paralysis of ciliary muscle), **treatment of bradycardia**.

Adverse effects:

Central nervous system: Causes hallucinations and delusions.

Cardiovascular system: Causes tachycardia.

Gastrointestinal tract: Decreases motility and decreases salivary secretion.

Lungs: Causes broncho-dilation and decreases airway secretion.

Urinary system: Blocks the muscarinic receptors causes muscle relaxation.

Lacrimation: Decreases lacrimation.

Contraindication: Atropine shouldn't be given to the patients with narrow angle glaucoma.

It causes **hyperthermia** in babies, and causes worsening of the **urinary retention** in patients with benign prostatic hyperplasia.

Benztropine: blocks the cholinergic receptors, it has anti-cholinergic properties. It is used for treatment of the Parkinson's disease.

Scopolamine: It is non-selective blocker of the cholinergic receptors. It is used to treat **motion sickness**.

Ipratropium/tiotropium: These are the respiratory drugs and used to treat **asthma** and chronic obstructive pulmonary disease **(COPD)**.

Glycolpyrolate: it is usually used to decrease the airway secretion peri-operatively

Oxybutynin: it relaxes the detrusor muscle in the bladder and used for **urinary urgency**, **mild cystitis** and **bladder spasm**.

Cholinergic drugs

Cholinergics are the drugs that act exactly as acetylcholine which is the primary neurotransmitter in the parasympathetic nervous system. Neurotransmitters are release in the body in response to depolarization. Acetyl CoA is added to choline and acetylcholine is formed which is stored in the vesicles inside the neurons. When the impulse comes from the central nervous system then acetylcholine is released and acts on cholinergic receptors which is of two types:

- M type (**muscarinic**) cholinergic receptors.
- N-type (**nicotinic**) cholinergic receptors.

When the acetylcholine activates the neuron or neuromuscular junctions then it is taken up by the acetylcholinestrase for destruction of acetylcholine. Cholinergic receptors are present in body:

- Parasympathetic pre-ganglionic neurons.
- Voluntary muscles of the body.

Direct acting cholinergic drugs:

- Bethanechol.
- Carbachol.
- Pilocarpine.
- Methacholine.

Mechanism of action:

Mechanism of action for the direct acting cholinergic drugs is the same as acetylcholine does it job in the body. They act on the cholinergic receptors.

- **Bethanechol** acts on the bowel muscles and specifically stimulates the bowel movements and best drug for the post operative ileus and it is also used for bladder contraction.
- **Carbachol** is used for glaucoma as it causes miosis and clears the trabecular meshwork.
- **Pilocarpine** is used in specifically for open angle glaucoma as it increases the ciliary muscle contraction and decreases the intraocular pressure and it also increases the secretion of lacrimal gland and salivary glands.
- **Methacholine** is used for the diagnosis of asthma.

Adverse effects:

Adverse effects are due to excessive acetylcholine secretion:

- Diarrhea/ decrease in blood pressure.
- Urination.
- Miosis.
- Bronchoconstriction.
- Excitation of skeletal muscle.
- Lacrimation.
- Salivation/sweating.

Indirect adrenergic agonists

Definition

Indirect adrenergic agonists stimulate the sympathetic system by any mechanism other than direct stimulation of alpha receptors.

Amphetamine

It releases the excess norepinephrine from the nerve terminal.

It is used in treating children with ADHD (attention deficit hyperactivity syndrome)

Ephedrine

It releases the excess norepinephrine from the nerve terminal.

It is used for treating urinary incontinence, bronchospasm and hypotension

Cocaine

It inhibits the re-uptake of norepinephrine after being release at the nerve terminal. This increases the concentration of nor epinephrine at the nerve terminal.

It is used for vasoconstriction, local anesthesia, drug abuse. Avoid beta blockers in cocaine overdose because it will block beta receptors and unopposed alpha activation.

ADP Inhibitors- Clopidogrel

Drug- Clopidogrel. Pasugrel, Ticagrel and Ticlopidine

Most commonly used is clopidogrel also called as clavis.

They inhibit platelet aggregation and Glycoproteins IIB/IIIA- so no primary hemostatic plug formation.

Uses-

- Acute Coronary Syndrome
- Coronary stent

Ticlopidine

- Causes neutropenia

Alpha and beta blockers

Sympathoplegics- these are agents that block the action of sympathetic NS.

Sympathetic hormones- norepinephrine and epinephrine- alpha (α1 and α2) and beta (β1 and β 2) receptors

BP = CO * TPR, CO = HR * SV

Alpha blockers	Beta blockers
Norepinephrine and epinephrine increase the heart rate by acting on SA node.	Beta receptors are on the heart muscle. Hence, .
	1. Non selective Beta blocker (β1 or β 2)- propanolol, timolol and nadolol
	2. Beta 1 selective- metaprolol, atenolol, acebutalol and esmolol
	3. Beta 2 selective-
	4. Alpha/beta blockers- carvedilol, labetolol

Mechanism of action-

Heart- Norepinephrine and epinephrine can cause an increase in the contractility and increase SV thereby increasing BP.

Kidney- renin is secreted under sympathetic NS. Rennin converts angiotensinogen to angiotensin1 and angiotensin converting enzyme converts angiotensin 1 to angiotensin 2. Angiotensin 2 causes increase in release of aldosterone which increases the sodium, water retention. Hence there is an increase in blood volume and therefore the BP is increased. Angiotensin 2 causes constriction of blood vessels.

Beta blockers decrease the cardiac output and the total peripheral resistance. Hence, lowers the blood pressure.

Uses

1. Hypertension
2. Angina- decreased perfusion to the heart.
3. Myocardial infarction
4. Anti-arrythmic – Sotalol (Class III Beta blocker)
5. Thyroid storms
6. Anxiety disorders

Adverse drug reactions

1. Impotence
2. Asthma- B2 receptors activated by epinephrine leading to bronchodilation

3. Bradychardia
4. Sedation
5. Sleep alteration

Alpha blockers

A1 receptors are found on blood vessels

A2 receptors are found on synaptic nerve terminals

Non selective Ablockers are called phentolamine and phenoxybenzamine.

Prazocin, doxazocin and terazocin

Mechanism of action-

They cause vasodilation and decrease PR so decrease BP.

Uses

1. Pheochromacytoma – phenoxybenzamine or phentolamine
2. Hypertension-
3. Benign prostatic hyperplasia- relaxes smooth muscles and help in urinary retention.

Adverse drug reactions

1. Orthostatic hypotension
2. Dizziness or light headedness

Alpha2 agonist medications

- Centrally acting sympathetic agents
- Bind to the alpha2 receptors- Decrease the release of norepinephrine from CNS.

I. Clonidine is used

- Uses- hypertension, smoking withdrawal symptoms, heroine/cocaine withdrawals.
- Side effects- dry mouth, rebound hypertension from abrupt withdrawal

II. Methyldopa

- Used to treat hypertension
- ADR- autoimmune hemolytic anemia
- Positive Coomb's test

Beta blockers and diabetics-

- Hypoglycemia
- Sweating, palpitations, tremors (mediated by epinephrine)
- Masked symptom

Antiarrythmics- Class1-4 drugs

Class I

[Police department questions][the little men][for prostitution]

Class Ia-

i. Procainamide- ventricular fibrillation, v. tachycardia, premature ventricular complex
Side effects- Lupus like syndrome (drug induced), pleuritis, pericarditis

ii. Disopyramide- it is a sodium channel blocker.
Has a stronger cholinergic effect.
Dry mouth, urinary retention, blurred vision, constipation
Torsedes de pontics- polymorphic

iii. Quinidine- it is from quinine. It blocks sodium channels. It prevents depolarization.
Uses- ventricular tachycardia, supraventricular tachycardia (atrial fibrillation, atrial flutter). Tachycardia can decrease cardiac output and lead to ischemia.
Side effects- prolong the QT interval, cinchonism- anticholinergic action-characterized by flushing, dizziness, constipation, dry mouth, blurred vision- overdose of quinidine. Another side effect is thrombocytopenia.

Class Ib-

i. Tocainide- ventricular arrhythmia
ADRs- bradycardia, AV node blockage, hypotension, ventricular tachycardia, bone marrow aplasia, palm fibrosis

ii. Lidocaine- sodium channel blocker and anesthetic
Uses- ventricular arrhythmia (vent. Tachycardia)
ADRs- CNS- drowsiness, nystagmus, slurred speech, convulsions (seizures)

iii. Mexiletine
ADRs- pancytopenia, nystagmus

Phenytoin- anticonvulsant. Sodium channel blocker

ADRs- CNS- nystagmus, ataxia, Gums- gingival hyperplasia

Class Ic- block sodium channels (ventricular myocyte, PURKINJE FIBRES)

i. Flecainide – supraventricular/ ventricular arrythmia
ii. Propafenone – brochospasm, bradycardia (blocks Beta blockers)

Antihypertensives: vasodilators

Hydralazine:

MOA- increase in cGMP- which causes smooth muscle relaxation- arteriole vasodilator- decreases BP

Arterioles autoregulate BP

Uses-

- CHF
- Hypertension

ADRs

- Hypotension
- Reflux tachycardia
- Peripheral oedema
- Lupus like symptoms (hydralazine and procainamide)

Minoxidil

MOA- potassium channel opener

Uses- hypertension

Side effects- hypertrichosis (excess hair)- help baldness. It can cause pericardial effusion.

Sodium nitroprusside

MOA- releases NO which increases cGMP- cause vasodilation (arterial)

Uses- hypertensive emergency, CHF, angina

Toxicity- Cyanide toxicity, hypotension

Diazoxide

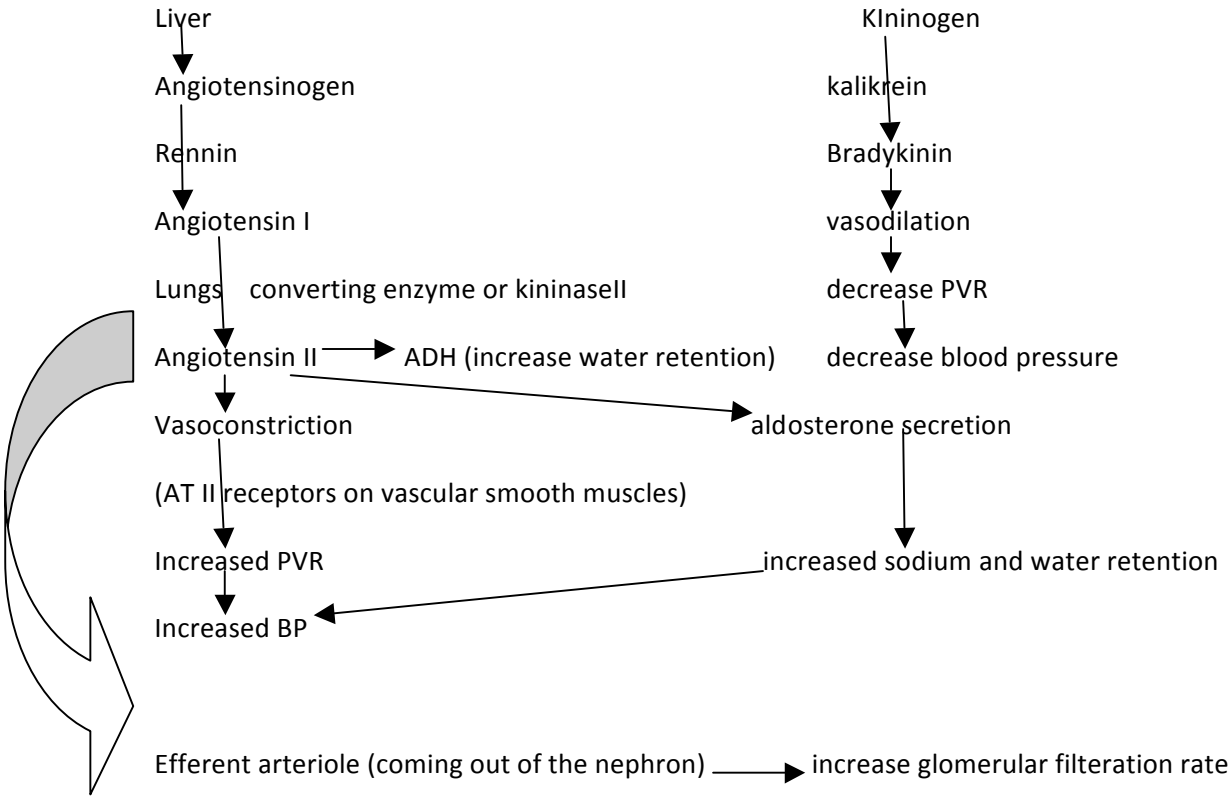
Potassium channel opener

ADRs- hypotension, hypoglycemia- blocks insulin release

Antihypertensives- ACE inhibitors

Drug name-

- Lisino**pril**
- Capto**pril**
- Enala**pril**



When ACE is inhibited Angiotensin I will not get converted to Angiotensin II and hence the BP will remain lowered. Bradykinin becomes inactive.

Uses

1. Hypertension
2. Congestive heart failure
3. Post MI patient

ADR

Cough –dry persistent- due to heavy bradykinin build-up

Angioedema- tongue and lips swollen

Postural hypotension

Teratogenic- not for pregnant- fetal malformation

Oh! It makes me dizzy

Proteinuria

Renal failure- bilateral renal stenosis

Increase K+- hyperkalemia

Low neutrophils

Angiotensin receptor blocker

Losartan

Uses- hypertension

ADR- hyperkalemia, fetal renal toxicity

Bile Acid Resins- Cholestyramine, Colestipol

Drugs

Cholestyramine and Colestipol and Colesevela

- They prevent intestinal reabsorption of bile acids.

LDL	HDL	Triglycerides
↑↑↑	↓	↓

- They taste horrible
- They cause GI discomfort.
- They decrease the absorption of fat soluble vitamins in terminal ileum.
- They cause cholesterol gall stones.

Calcium channel blockers

Definition- They block calcium channels.

Cardiac membrane depolarized- Beta 1 receptors- cyclic AMP formation- protein kinase A- L type calcium channel phosphorylation.

Calcium binds with troponin-tropomyosin complex

Calcium sent to extracellular space through Ca-Na exchanger.

Summary- Calcium is brought from anti-d cells to bind to troponin-tropomyosin complex for the myocardial contraction to happen.

Calcium channel blockers can be of two types-

Dihydropyridines	Non- Dihydropyridines
Nifidipine, Amlodipine, Nimodipine	Diltiazam, Verapamil
Act on vascular musculature preferably	Act on heart muscles
	Negative ionotropes
	Direct effect on SA and AV node
	Decrease in afterload and preload and thereby decrease in BP

Clinical applications-

1. Hypertension
2. Arrhythmias- Atrial fibrillation
3. Prismetal angina- vasospasm of coronary artery- drug used Diltiazam or Verapamil
4. Raynaud's phenomenon

Side effects-

1. Bradycardia
2. Peripheral edema- mostly nifidepine or amlodipine
3. Flushing and dizziness
4. Hypotension
5. Constipation

Cilostazol/ Dipyramydole (persantine)

- Phospohodiesterase III inhibitors
- Decrease platelet aggregation

Uses-

- Intermittent claudication- in old patients with lot of leg pain with hypocholesterolemia, CAD, diabetes and hypertension it is used.
- Coronay vasodilation
- Prevention of stroke especially when taken with aspirin

Toxicity

- Hypotension
- Headaches
- Nausea
- Facial flushing
- Abdominal pain

Class II, III and IV antiarrythmic drugs

Class II

- Beta blockers
- Sotalol, propanolol, esmolol
- MOA- block beta receptors, Sotalol- decreases automacity, slows down AV/SA node
- Block potassium channel

Uses

- Supraventricular arrhythmia- atrial flutter, atrial fibrillation
- Ventricular arrhythmia

Esmolol

- Short acting adrenergic beta-blocker
- Surgical ankylosis

Class III antiarrythmic drugs

- Potassium channel blockers

Amiodarone

- Refracting atrial fibrillation or atrial flutter.
- Ventricular tachycardia

ADRs-

- Pulmonary fibrosis (restrictive lung disease)
- Hyper/hypothyroidism
- Liver- hepatocellular necrosis
- Corneal microdeposits/ photosensitivity

Bretylium

Uses – refractory ventricular fibrillation/ Ventricular tachycardia

ADRS- hypotension

Class IV

- **Calcium channel blockers**

1. Verapamil
2. Diltiazam
3. Nifidepine
   MOA- block L-type calcium channels and slows down AV/SA node

Uses

Supraventricular arrhythmia- atrial fibrillation, atrial flutter

Side effects

- Bradycardia
- Hypotension
- Dizziness
- Constipation

Miscellaneous

Magnesium sulfate- stabilize cardiac cell membrane

Uses-

- Torsades de pointes
- Digoxin indiuced arrhythmia

Side effects

- Paralysis
- Respiratory paralysis
- Flushing/ headache

Adenosine

Activates acetylcholine sensitive K+ channels in SA/AV nodes

Uses-

- Supraventricular tachycardia

Side effect- chest pain, dypsea, flushing, headache

Digoxin

- It is a cardiac glycoside.
- Mainly used for CHF and atrial fibrillation
- Digoxin works on cardiac myocytes.
- **MOA**- it is a sodium-pottasium ATPase pump inhibitor. Digoxin competes with potassium in sod/pots ATPase channel.
- CHF- they have thin muscle. Digoxin increases contractility.
- Atrial fibrillation- HR 120-150. Digoxin increases parasympathetic activity. It activayes the vgus nerve. Digoxin binds AV node and slows down the heart rate.
- 75% of digoxin is bioavailable.
- 20-40% is bound to protein. IT TAKES 40 HOURS TO BE USED UP IN THE SYSTEM.
- **ADRs**- It has a narrow therapeutic index. It can cause-
  1. Arrhythmias- increase the PR interval, decrease the QT interval, scooping of the ST segment.
  2. Bradycardia
  3. Blurry yellow vision, nausea, vomiting, diarrhea
  4. Renal failure
  5. Hypokalemia – worsens digoxin toxicity.
- **Treatment**-
  1. Slowly reduce K level when it becomes K=2.5
  2. Lidocaine
  3. Anti-Fab fragment (antidigoxin antibody fragment)
  4. Magnesium

Diuretics

Hypertension can be of 2 types- essential (95%) and secondary(5%)

Risk factors

- Obesity
- Family history
- Race- African American
- Physical inactivity
- Cigarette smoking

Essential- idiopathic

Secondary-

- Renal artery stenosis
- Fibromuscular dysplasia more in white or younger people
- Cushing syndrome
- Primary aldosteronism
- Hyperthyroidism
- Coarctation of aorta

Malignant hypertension-

- End organ damage-
- Heart- MI, aortic dissection
- Lungs- pulmonary oedema,
- Kidneys- nephropathy, increased BUN/CReatinine
- Eyes – hemorrhages and
- CNS – seizures, strokes, encephalopathy

Antihypertensives

- Diuretics
- ACE inhibitors
- Beta blockers
- Vasodilators

Diuretics

- Dieresis- urinate
  A. Hydrochlorothiazide- inhibits reabsorption of Na and CL into distal convoluted tubules. they urinate a lot

     clinical uses-

- hypertension
- congestive heart failure
- idiopathic hypercalciuria- when patient has hypercalcemia- normal saline is given, do not give thiazides as the condition worsens
- nephrogenic diabetes insipidus

side effects-

1. HYPER GLUC

HYPER - Glycemia, Lipidemia, Uricemia, Calcemia

2. hyponatremia
3. hypokalemia

Contraindicated in patients with sulpha allergies

B. Furesamide

- Lasix- last six hours
- Loop diuretic- thick ascending loop of Henle
- Inhibits the co-transport of Na/K ions

Uses

- Hypertension
- Congestive heart failure
- Pulmonary oedema
- Cirrhosis
- Hypercalcemia

ADR

- Ototoxicity
- Hypokalemia, hypotension
- Dehydration
- Allergy
- Nephritis (intestinal)
- Gout

Metabolic alkalosis

Familial Dyslipidemia

Type I hyperchylomicronemia-

- Autosommal recessive genetic mutation
- Lipoprotein lipase deficiency or apolipoprotein C2 mutation
- Deficiency causes increase in levels of chylomicrons
- Pancreatitis- abdominal pain radiating to the back. The pneumonic is GET SMASHED (gall stones, ethanol, trauma, scorpion bite, mumps, high triglyceride levels.
- They develop hepatomegaly and splenomegaly
- They develop eruptive xanthomas.

Type IIa Familial hypercholesterolemia

- Autosommal dominant mutation
- Decreased LDL receptors
- High levels of LDL and cholesterol
- Accelerated atherosclerosis
- A lot of xanthomas (archillius tendon)
- Corneal arcus

Type IV hypertriglyceridemia

- Autosommal dominant
- Excess production of VLDL
- Increase in VLDL and triglycerides

Abetalipoproteinemia

- Autosommal recessive mutation in MTP (microsomal triglyceride transfer protein) gene.
- Biopsy has to be taken- lipid accumulation within their enterocytes.
- Failure to thrive.
- Steatorrhea- greasy looking stool.
- Develop acanthocytosis, ataxia and night blindness.

Fibrates

Drugs

- Genfibrosil
- Clofibrate
- Bezofibrate
- Fenofibrate

MOA- fibrates mediate gene expression using PPAR (peroxisome proliferation activated receptors)

- It increases the HDL and ApoAI and ApoAII lipoproteins. It decreases the tri acil glyceride (TAG) levels
- Side effects- myositis- muscle inflammation and hepatotoxicity (increased liver function toxicity).
- Cholesterol gall stones.

Cholesterol absorption blockers

- Prevent reabsorption of cholesterol in small intestine border
- Drug- ZETMINE
- Decrease in LDL

Glycoproteins IIA/IIIB inhibitors

Drugs-

- Abciximab (ATE for drugs)
- Eptifibatide
- Tirofiban

Mab- monoclonal antibody.

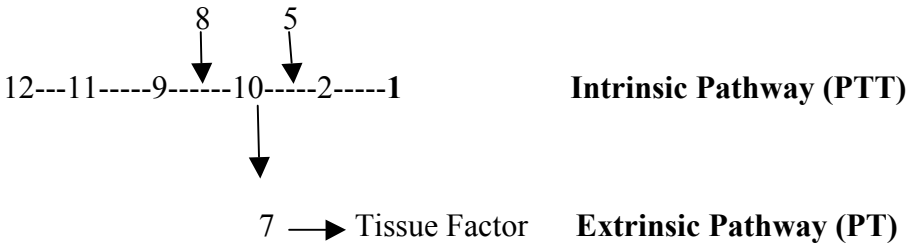
MOA- binds to GPIIB and IIIA on activated platelets- decrease platelet aggregation.

Uses-

- Acute coronary syndrome like ST elevation MI and also
- percutaneous coronary angioplasty.
- Bleeding
- thrombocytopenia

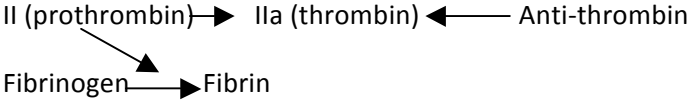
Heparin- anticoagulants

Clotting cascade



MOA

It acts as a co-factor for activation of anti-thrombin



Decrease in thrombin leads to decrease in clot formation.

Decrease in factor Xa- will not cause clot formation.

Clinical uses-

1. Immediate anticoagulation for pulmonary embolism.- clot formed in the deep veins of the legs (proximal aspect) in patients who are suffering from cancer, immobile or have undergone recent surgery. Pulmonary embolism causes hypoxemia.
2. Acute coronary syndrome- myocardial infarction
3. Deep venous thrombosis – veins in legs
4. Pregnant patients can be given heparin as it does not cross the placental barrier.
   PTT is monitored to monitor heparin. If PTT is high patient is well anticoagulated.

Toxicity

1. Bleeding
2. Heparin induced thrombocytopenia (HIT)- Heparin induces low platelet. Pathophysiology- platelet factor 4 to which heparin normally binds. IgG binds to these platelets.
3. Protamine sulphate is given for heparin toxicity.

Low molecular weight heparin- Enoxaparin and Dalteparin- subcutaneous heparin is LMWH which is injected into the skin. They have a longer bioavailability. They have 2 to 4 times more half-life than their IV form.

Drugs available for HIT-

1. Lepuridin
2. Bivaluridin

   These 2 are derivatives of Hirudin found in leeches which is a thrombin inhibitor.

Introduction to Antiarrythmic drugs

Arrhythmia is the number 1 cause of death. (US)

Cell membrane of myocyte has ion channels like

1. Sodium channel
2. Calcium channel
3. Potassium channel

4 stages of cardiac depolarization

Stage4- slow influx of sodium from SA node into cell. Negative 80 to negative 40. It is enough for propogation of action potential

Upstroke depolarization- a high influx of sodium ions

There is a small drop after that because of influx of calcium ions. Ca ions are released from sarcoplasmic reticulum. Calcium is needed for contraction. A little bit of K influx is also there.

Rapid repolarisation- K efflux rapidly

P wave-atrial depolarization

QRS complex- ventricular depolarization

T wave- ventricular repolarization

Antiarrythmic drugs

Class I (A,B,C)- block sodium channel receptors **NO**

Class II- Beta blockers- blocks beta receptors **BAD BOYS**

Class III- blocks potassium channels **PASSES**

Class IV- calcium channel blockers **COPS**

Lipoprotein Metabolism Physiology

Lipoproteins are lipids carrying proteins.

The various types-

- Chylomicrons
- LDL- more cholesterol
- IDL
- HDL- more cholesterol

Chylomicrons are lipoproteins that transport fat from gut to the liver or the adipose tissue.

- Fat is composed of triglyerides (glycerol+ fatty acids)
- CCK in duodenum activate gall bladder to contract to emulsify to convert fat into fat droplets which reach enterocytes.
- Chylomicrons are composed of proteins on the outer side with APO-B48 protein which is integrated protein.
- Chylomicrons can go to adipose tissue or liver.
- In adipose tissue, lipoprotein lipase is present which is activated by apoprotein C2.
- After activation the triglycerides are broke down to glycerol and fatty acids.
- Whatever remains of the chylomicrons is called a chylomicron remanant.
- The remnants bind to apoE and get reabsorbed.
- In liver, chylomicrons bind to the LDL receptor on the hepatocyte. Liver cells use apoE to bind to the liver.
- There all the triglycerides are taken up by the liver. There is hepatic triglyceride lipase

LDL or low density lipoprotein- fat is taken up by liver and converted to VLDL

- Cholesterol ester(hydrophilic) is different from cholesterol.
- VLDL has apoB121 and then it picks up peripheral proteins apoE and apoC
- VLDL bind to apoC when it reaches adipose tissue and lipoprotein lipase breaks them down to fatty acids and glycerol.

IDL or intermediate density lipoprotein

- If VLDL continues in blood and binds to more lipoprotein lipase, when only 30% of triglycerides is left in VLDL it is called IDL.
- It has more cholesterol esters.

LDL or low density lipoprotein

- When only 10% of triglycerides is present within the VLDL it is called LDL.
- It has more amount of cholesterol esters.
- It has lost 2 peripheral proteins.

- LDL is called lousy proteins
- High levels of LDL can be oxidized by free radicals. In the blood vessels, LDL gets deposited in the endothelium basement membrane- this result in a plaque formation- atherosclerosis occurs.
- When plaque ruptures- clot formation occurs
- LDL can cause MI or acute ischemic stroke, mesenteric ischemia, claudication, coronary artery disease
- Hyperlipidemia

HDL

- It has ApoA- integral protein
- HDL needs LCAT(lecithin cholesterol acil transferase) enzyme to esterify cholesterol
- HDL with LCAT is called matured HDL
- Cholesterol esters are dumped into liver where they are converted to bile acids.
- Exercise can increase HDL levels.

Niacin (Nicotininc acid)

- It is Vit B3
- It inhibits lipolysis in adipose tissue, thus reducing the hepatic VLDL secretion in circulation.
- There is a decrease in LDL level.
- It increases HDL and lowers triglyceride level.
- Side effects- red facial flushing- due to vasodilation of blood vessels.- to decrease facil flushing aspirin is given 30 to 60minutes before.
- It can also cause hyperglycemia (can lead to acanthosis negricans) and hyperurecmia- it can worsen or lead to gout

Statins

- Patients with high triglycerides, high LDL and low HDL are predisposed to coronary artery disease.
- Other risk factors- cigarette smoking, obesity, hypertension and diabetes.
- Lifestyle can cause increase in cholesterol- lack of exercise or high intake of saturated fatty acids.
- Diet and exercise are first line of treatment.

Drugs- lovastatin, prevastatin, atorvastatin, rosavastatin, simverstatin

- These are lipid lowering drugs.
- HMG CoA reductase- converts HMG CoA to mevalonic acid (which is used to make cholesterol) in hepatocyte
- Statins inhibit the action of HMG CoA reductase so cholesterol synthesis is reduced in the liver.
- Effects are

LDL	HDL	Triglycerides
▲▲▲	▼	▼

- These cause a decrease in mortality.
- Side effects- Myopathy- Rhabdomyolysis- break down of muscle cells.- elevated levels of CK.
- It can also cause hepatotoxicity- AST and ALT lvels need to be checked. They can be high due to statins
- Contraindication- children, teenagers or pregnant females

Thrombolytics- tPA (Alteplase)

- Alteplase –tPA- tissue plasminogen activator
- Retiplase-rPA
- Tenectiplase-Tak-tPA
- Has effect on PT and PTT but not on platelets

Uses

- Early MI
- Early ischemic stroke
- Severe pulmonary emboli

Toxicity

- Bleeding
- History of intracranial bleeding- do not give tPA
- Severe hypertension- contraindication
- Amino capric acid- to deal with tPA toxicity

Warfarin

- Affects factors 2,7,9 and 10
- All coagulation factors are made in the liver.
- Vit. K oxidized converted into reduced form by epoxide reductase.
- The reduced VitK activate factors II, VII, IX and X and protein C and S to form mature cofactors
- **VItK was born in 1972**
- Warfarin inhibits epoxide reductase so inhibits extrinsic pathway.
- It interferes the synthesis and gamma carboxylation of the cofactors.
- Check the PT /INR to know the level of anticoagulation. 2-3
- Warfarin has a long half-life. It is also called Coumadin.

Uses

- Chronic anti-coagulation- STEM-I
- DVT prophylaxis
- Protection and prevention of stroke in patients with atrial fibrillation.
- We **cannot give** warfarin to pregnant patients.

Complications

- Bleeding
- Teratogen
- Induce skin necrosis

Overdose treatment

- Vitamin K
- Fresh frozen plasma- factors II VII IX and X

Anti-histamines:

These are the drugs that blocks or reverses the actions of histamines.

Antihistamines:

There are two types of anti-histamines:

- H1 blockers.
- H2 blockers.

H1 blockers:

There are two kinds of H1 blockers:

- First generation.
- Second generation.

First generation drugs:

First generation drugs are very sedative because they cross the blood brain barrier.

1. Diphenhydramine.
2. Dimenhydrinate.
3. Chlopheramine.

Clinical uses:

- Allergies.
- Pruritis.
- Motion sickness.
- Sleep aid.

Side-effects:

- Anti-cholinergic
    1. Dry mouth.
    2. Constipation.
    3. Urinary retention.

Second generation drugs:

These drugs are less sedative than first generation and used to treat allergies.

- Loratidine.
- Fexofenadine.
- Desloratidine.
- Cetirizine.

Asthma:

Asthma drugs:

Asthma pathophysiology:

Asthma patients are exposed to dust and pollens. These dust and pollens are attached to IgE and these IgE are attached to the mast cells and mast cells release leukotriene and histamines and causes symptoms like bronchoconstriction and chest tightness this is the early response and late response occurs because of inflammatory substances.

Isoproterenol:

Isoproterenol is non-specific beta agonist. It is a medication use to treat asthma and decreases the smooth muscle tone and causes smooth muscle relaxation.

Side effects:

- Tachycardia.

Albuterol:

It is very common medication used to treat asthma. It is beta2 agonist and relax the smooth muscles.

Mechanism of action:

It increases the concentration of cAMP and causes smooth muscle relaxation.

Salmeterol:

It's a long acting medication means it has longer duration of action.

Side effects:

- Arrhythmias.
- Tremors.

Methylxanthines:

These are theophylline derivatives.

Mechanism of action:

Thiophylline inhibits phosphodiestrase and inhibition of phosphodiestrase causes decrease degradation of cAMP and causes bronchodilation.

Side effects:

These drugs have very narrow therapeutic index.

- Seizures.
- Cardiotoxic.

Theophylline toxicity is treated by “Activated charcoal”.

Muscarinic antagonist:

Ipratropium is muscarinic antagonist used to dilate bronchioles in case of asthma.

Clinical use:

- Chronic obstructive pulmonary disease (COPD).

Cromolyn:

Cromolyn is mast cell inhibitor. It prevents the secretion of leukotriene from the mast cells.

Clinical use:

- Prophylaxis of asthma.

Corticosteroids:

Steroids are anti-inflammatory drugs. Steroids prevent the activation of cytokines.

- Fluticasone.
- Beclomethasone.
- Prednisone.

Clinical use:

- Chronic asthma.

Anti-leukotriene:

- Zileutin-5 lipoxygenase pathway inhibitor.
- Zafirlukast, montelukast-blocks the leukotriene receptor.

Clinical use:

- Aspirin induced asthma.

Expectorants:

Expectorants allow you to expel something out of the lungs.

Expectorants:

Guafenasin (robitussin):

Removes excess sputum from the lungs but does not suppress the cough reflex.

N-acetylcystein-mucolytic:

This drug degrades the thick sputum and then sputum is coughed out by the patient.

Clinical use:

- Cystic fibrosis.
- Antidote for acetaminophen toxicity.

Anti-psychotics (neuroleptics)

Psychosis:

Psychosis is distorted perception of reality and it is characterized delusions and hallucinations (visual, auditory).

Anti-psychotic drugs:

Typical anti-psychotics:

- Haloperidol.
- Chlorpromazine.
- Fluphenazine.
- Trithioperazine
- Thioridazine.

Mechanism of action:

They block dopamine receptors (D2).

Indications:

- Schizophrenia:

  Positive symptoms are:

  1. Delusions.
  2. Hallucinations (auditory).
  3. Disorganized/catatonic behavior.
  4. Disorganized speech.

  Negative symptoms are:

  1. Flat affect.
  2. Social withdrawal.
  3. Lack of motivation.
  4. Lack of speech/thoughts.
- Psychosis.
- Acute mania.
- Tourettes syndrome.

Typical anti-psychotic drugs are primarily used for treatment of positive symptoms of the schizophrenia.

Toxicity:

- Extra-pyramidal:
  1. Acute dystonia (after 4 hours).
  2. Akithisia(restless leg syndrome) –after 4 days.
  3. Bradykinesia (after 4 weeks).
  4. Tardive dyskinesia (after 4 months).
- Anti-cholinergic:
  1. Dry mouth.
  2. Constipation.
  3. Urinary retention.
- Alpha blockade:
  1. Hypotension.
- Histamine:

  They block histamine receptors and cause sedation.

- Endocrine:
  1. Hyperprolactinemia.

High potency drugs:

- Haloperidol.
- Trithioperazine.
- Fluphenazine.

Low potency drugs:

- Thioridazine.
- Chlorpromazine.

Neuro-leptic malignant syndrome:

This is characterized by following clinical features:

- Hyper-pyrexia.
- Rigidity.
- Myoglobinuria.
- Autonomic instability.

Treatment:

Patients with this syndrome should be treated with:

- Dantrolene.
- Bromocriptine.

Atypical antipsychotics

Atypical anti-psychotic drugs:

Difference between typical and atypical anti-psychotics is the side effects caused by them. Typical anti-psychotics cause more extra pyramidal side effects as compared to atypical anti-psychotics.

- Olanzapine.
- Risperidone.
- Quetiapine.
- Clozapine
- Aripiprazole
- Ziprasidone

Mechanism of action:

Atypical anti-psychotics act on following receptors:

- Serotonin receptors.
- Dopamine receptors blockers.
- Alpha1 receptors.
- H1 receptors.

Uses:

- Schizophrenia (both positive and negative symptoms).
- Bipolar disorder.
- Depression.
- Obsessive compulsive disorder.
- Anxiety.
- Tourette syndrome.
- Mania.

Toxicity:

- Olanzapine/clozapine causes significant weight gain.
- Clozapine causes agranulocytosis (watch WBC weekly).
- Ziprasidone causes prolonged QT interval.

Antidepressants

Antidepressants are the drugs used to treat depression. Depression is actually opposite of happiness. It is characterized by extreme sadness, general loss of interest in daily activities, insomnia, and change in appetite and loss of self-esteem.

Mechanism of depression

The depression is a condition caused by deficiency of neurotransmitters i.e. norepinephrine, dopamine and serotonin.

Clinical manifestation

Sleep disorders

Interest (loss of)

Guilty feeling

Energy loss

Concentration loss

Appetite loss

Psychomotor agitation

Suicidal thoughts

Tricyclic anti-depressants (TCAs)

Depression:

Depression is a state of mind where brain is having low levels of following neurotransmitters:

- Serotonin and Nor-epinephrine.

Tricyclic anti-depressants (TCA):

- Clomipramine.
- Amoxepin.
- Doxepin/desipramine.
- Imipramine.
- Nortryptyline.
- Amitriptyline.

Mechanism of action:

Tricyclic anti-depressants inhibit the re-uptake of norepinephrine and serotonin and increases the levels of these neurotransmitters in the synapse.

Uses:

- Depression.
- Enuresis.
- Obsessive compulsive disorder.

Side effects:

- Alpha1 receptor blockade:
  1. Orthostatic hypotension.
- Anticholinergic effects:
  1. Tachycardia.
  2. Dry mouth.
  3. Urinary retention.
  4. Hallucinations.
  5. Confusion.
- Toxic over dose:
  1. Coma.
  2. Convulsions.
  3. Cardiotoxicity.

     Sodium bicarbonate is used to reverse the TCA overdose toxicity.

Selectve serotonin reuptake inhibitors (SSRIs)

Selective serotonin reuptake inhibitors (SSRIs):

Drugs name:

- Fluoxetine.
- Paroxetine.
- Escitalopram.
- Citalopram.
- Sertraline.

Mechanism of action:

These drugs inhibit the reuptake of the serotonin in the presynaptic neuron.

Uses:

- Depression.
- Generalized anxiety disorder.
- Panic attacks.
- Obsessive compulsive disorder.
- Bulimia.
- Post-traumatic stress disorder.
- Social phobias.

Toxicity:

- Sexual dysfunction (anorgasmia).
- Dystonic reaction.
- Serotonin syndrome:
    1. Hyperthermia (temperature >40C)
    2. Muscle rigidity.
    3. Confusion.
    4. Cardiovascular collapse.
    5. Flushing.
    6. Diarrhea.
    7. Seizures.

Drug of choice to treat the serotonin syndrome is cyproheptadine.

Serotonin Norepinephrine reuptake inhibitors SNRIs

It is a group of antidepressant drugs that include:

Duloxetine

Venlafaxine

Desvenlafaxine

Mechanism of action

It increases the concentration of serotonin and norepinephrine in the synaptic cleft by inhibiting the reuptake of serotonin and norepinephrine respectively.

Use

Generalized anxiety disorders (venlafaxine)

Depression

Diabetic neuropathy (duloxetine)

Toxicity

Raised blood pressure

Nausea

Stimulation

Sedation

Atypical anti-depressants

Atypical anti-depressants:

Atypical anti-depressants are:

- Bupropion.
- Mirtazapine.
- Maprotiline.
- Trazodone.

Mechanism of action:

Bupropion Increase the secretion of nor-epinephrine/dynamic.

Uses:

- Smoking cessation.
- Major depression.

Toxicity:

- Stimulant effect.
- Tachycardia.
- Insomnia.
- Headache
- Seizures-bulimic patients.

Mirtazapine:

Mirtazapine is alpha 2 receptors blocker. These receptors are present on the pre-synaptic neuron.

Uses:

- Major depression.
- Patients have insomnia.

It is good in cachectic or elderly patients.

Toxicity:

- Weight gain.
- Dry mouth.
- Sedation.

Maprotiline:

It prevents the re-uptake of the nor-epinehprine and also used to treat major depression.

Toxicity:

Orthostatic hypotension:

Trazodone:

It inhibits the re-uptake of the serotonin.

Uses:

It is used for:

- Major depression.
- Insomnia.

Toxicity:

- Priapism.
- Nausea.
- Orthostatic hypotension.
- Sedation.

Lithium

Lithium:

Mechanism of action:

Mechanism of action is unknown, possibly by inhibition of the phosphoinositol cascade (IP3).

Uses:

Lithium is used for:

- Mood stabilizing (for bipolar patients).
- Syndrome of inappropriate anti diuretic hormone (SIADH).
- Prevention of acute maniac attacks.

Toxicity:

- Tremors.
- Sedation.
- Edema.
- Heart block.
- Hypothyroidism.
- Polyuria (ADH antagonist).
- Teratogenic:
    1. Fetal heart defects.
    2. Malformation of great vessels.

Drug interactions:

Lithium interacts with following drugs:

- Thiazide diuretics.
- Non-steroidal anti-inflammatory drugs (NSAIDs).

Monoamine oxidase inhibitors (MAOIs)

Drug names:

- Tranylcypromine.
- Isocarboxazide.
- Phenelzine.
- Selegiline.

Mechanism of action:

These drugs inhibits the monoamine oxidase and increases nor-epinephrine and dopamine.

Uses:

- Atypical depression.
- Hypochondrosis.
- Anxiety.

Toxicity:

- Hypertensive crisis.

Drug interactions:

- Tyramine .
- Selective serotonin re-uptake inhibitors (SSRIs).
- Tricyclic anti-depressants.
- Meperidine.
- St. john’s herb.
- Dextromethophan.

Anticonvulsant drugs

The anticonvulsant drugs are used to treat seizure. A seizure is an abnormal synchronous electrical depolarization of neuron in the central nervous system. Different types of drugs are used in different type of seizures.

Types of seizures

1. Partial seizures

Partial seizure occur due to focal neuronal discharge in any part of cerebral cortex that elicits focal neurological signs. It can be of two types:

i. Simple partial seizure
ii. Complex partial seizure (associated with loss of consciousness)

2. Generalized seizures

Generalized seizures have their origin throughout the cerebral cortex and it can be of following types:

i. Generalized tonic clonic seizure: The tonic phase is associated with loss of consciousness, generalized body rigidity, loss of control over fecal and urinary sphincters. The clonic phase is characterized by sudden, jerky movements of muscles of the body.

There many other type of seizures that may prevail:

3. Absence seizure

Usually predominant in children and is complained by the teacher.

4. Myoclonic seizure

Small portion or group of muscles show seizure

5. Febrile seizure

High grade fever i.e. 105 degree Fahrenheit can cause this type of seizure is children or infants

6. Epileptic seizure

These are recurrent seizures with period of complete consciousness between the two episodes of seizure

Barbiturates

It is an anticonvulsant drug that can be used for other conditions. Barbiturates is a drug class and includes:

i. Phenobarbital
ii. Pentobarbital
iii. Thiopental
iv. Secobarbital

Mechanism of action

The barbiturates facilitate the GABA action by increasing the duration of the chloride ion channel opening.

Uses

First time used in children with simple or generalized seizures

Sedation for anxiety

Insomnia

Induction of anesthesia (thiopental)

Benzodiazepines

Benzodiazepines:

- Diazepam.
- Lorazepam.
- Clonazepam.
- Alprazolam.
- Oxazepam.
- Triazolam.
- Chlordiazepoxide.

Mechanism of action:

Benzodiazepines facilitate GABA action and increase the frequency Chloride channel opening.

Uses:

- Seizures (status epilepticus).
- Muscle spasm.
- Alcohol withdrawal-delirium tremens.
- Anxiety.
- Night terror
- Sleep walking.
- Hypnotic (insomnia).

Toxicity:

- CNS depression.
- Dependence.
- Addiction.

Toxicity from over-dose of the benzodiazepines is treated with flumazenil which is a competitive antagonist of the GABA receptors.

Carbamazepine

Carbamazepine:

It prolongs the inactivated state of the sodium channel.

Uses:

- Partial seizures.
- Tonic-clonic seizures.
- Trigeminal neuralgia.

Toxicity:

- Diplopia.
- Agraulocytosis.
- Aplastc anemia.
- Liver toxicity.
- Teratogenic.
- Steven-johnson syndrome.
- Syndrome of inappropriate anti diuretic hormone (SIADH).

Ethosuximide

It is an anticonvulsant drug

Mechanism of action

It blocks thalamic T-type calcium channels

Uses

Absence seizures in children (first line agent)

Side effects

Fatigue

GI distress

Headache

Stevens Johnson syndrome

Gabapentin

Mechanism of action

It inhibits the high voltage Ca (calcium) channels. Thus neurotransmitter secretion is inhibited and thus neuronal firing is slowed down.

It is also GABA analog and acts on GABA channels and inhibit the post synaptic neuronal firing.

Uses

Partial seizures i.e. simple and complex partial seizures

Generalized tonic-clonic seizure

Peripheral neuropathy i.e. burning or tingling sensations in diabetic nephropathy

Post herpetic neuralgia

Migraine prophylaxis

Bipolar disorder

Toxicity

Sedation

Ataxia

Lamotrigine

It is an anticonvulsant drug.

Mechanism of action

It inhibits the voltage dependent Na channels in the presynaptic neurons and thus prevents repetitive firing of neurons.

Pharmakokinetics

It is metabolized in the liver

Uses

Partial seizures i.e. simple partial and complex partial seizures

Generalized tonic-clonic seizures

Side effects

Steven Johnson syndrome

Leviteracetam

It is an anticonvulsant drug

Mechanism of action

It modulate the GABA and glutamate release. It is supposed that leviteracetam increases the GABA concentration and decrease the glutamate concentration at the synaptic cleft.

Uses

It prevents

- Simple partial seizure
- Complex partial seizure

It is also used to treat

- Tonic-clonic seizure

Parkinson's drugs

Parkinsonism:

Parkinsonism is a movement disorder. Substantia nigra is the basal ganglia which contains dopaminergic neurons and that synthesizes the dopamine in the brain. Tyrosine is converted into DOPA and which is further converted into dopamine by the action of an enzyme dopa-decarboxylase. Dopamine is stored in the vesicles in the pre-synaptic neuron and when an impulse comes the vesicles are fused and they are emptied into the synapse and attaches to the dopamine receptors (D1 and D2) on the post synaptic neuron and after the dopamine release when the impulse is over then released dopamine is either degraded or reuptake into the pre-synaptic neuron by the help of the catechol-o-methyl transferase and monoamine oxidase.

Pathophysiology:

Parkinsonism is due to the depletion of the dopaminergic neurons in the substantia nigra which has the inhibitory effect in the brain and as the dopamine neurons are depleted the action of the acetylcholine neurons is increased and imbalance of the dopaminergic neurons and acetylcholine neurons causes the symptoms of the disease.

Symptoms of Parkinsonism:

- Tremor (resting 'pill rolling tremors').
- Rigidity.
- Akinesia/bradykinesia.
- Postural instability.

Drugs used for Parkinsonism:

Drugs used for the Parkinsonism works on following two principles:

1. Drugs that increases the dopamine.
2. Drugs that decreases the cholinergic activity.

Drugs commonly used are:

- Levi-dopa/carbidopa.
- Bromocriptine.
- Amantadine.
- Mono-amine oxidase inhibitors.
- COMT inhibitors (entacapone).
- Anti muscarinics (benztropine).

Levi-dopa:

Mechanism of action:

Levi-dopa is a metabolic precursor to dopamine. Dopamine cannot cross the blood brain barrier that's why levi-dopa is given and levi-dopa is not given alone to prevent its decarboxylation peripherally and given in combination with carbidopa and it inhibits the dopa decarboxylase and decreases the peripheral decarboxylation to dopamine.

Drug interactions:

- Monoamine oxidase inhibitors are not given along with dopamine as it causes life threatening hypertension.
- Vitamin b6 increases the decarboxylation of levi-dopa peripherally.
- Antipsychotics occupy dopamine receptors.

Side-effects:

- Nausea.
- Vomiting.
- Arrhythmias.
- Postural hypotension.
- Dyskinesia.
- Hallucinations.

Carbidopa:

Mechanism of action:

Carbidopa inhibits dopa-decarboylase in the periphery and in this way it increases the bioavailability of the levi-dopa to the brain.

Dopamine agonists:

Two types of dopamine agonists are available:

- Ergot derivatives e.g. bromocriptine.
- Non-ergot derivatives e.g. pramipexole

Mechanism of action:

They bind to dopamine receptors specifically D2. These are the second line agents. These are used in conjunction with levi-dopa. Bromocriptine is also used to treat Hyperprolactinemia.

Side effects:

- Hallucinations

- Delirium.
- Cardiac arrhythmias.

Amantadine:

Amantadine is the antiviral but also increases the dopamine release in the brain. It is also used to treat influenza A and rubella.

Toxicity:

- Ataxia.

Selegiline:

Mechanism of action:

Selegiline is selective mono amine oxidase type B inhibitor. It inhibits the reuptake of the dopamine in the synapse and in this way the dopamine is increased in the synapse. Dopamine is reuptake by monoamine oxidase type B and converted into DOPAC.

Catechol-o-methyl transferase inhibitors (COMT):

These drugs inhibit the dopamine degradation in the synapse by inhibiting the catechol-o-methyl transferase enzyme.

Antimuscarinic drugs:

These drugs inhibit the cholinergic activity and use as an adjuvant in parkinsons disease therapy.

Effects:

These agents primarily reduce:

- Tremor.
- Rigidity.
- Akinesia.

Side effects:

- Decreases the parasympathetic response.
- Sedation.
- Dry mouth.
- Constipation.
- Mental confusion.
- Urinary retention.

Phenytoin

Phenytoin

Mechanism of action:

Phenytoin binds and inactivates the sodium channels and prevents the depolarization of the neuron.

Uses:

- First line drug for tonic clonic seizures.
- Prophylaxis for status epilepticus.
- Simple/complex seizures.

Toxicity:

- P450 inducer.
- Hirsutism.
- Enlarged gums-gingival hyperplasia.
- Nystagmus.
- Yellow browning of the skin.
- Teratogenic-“fetal hydantoin syndrome”.
- Osteomalacia.
- Interfere with folate absorption-“megaloblastic anemia”.
- Neuropathy-ataxia, vertigo, headache.

Tiagabin

It is an anticonvulsant drug

Mechanism of action

It inhibits GABA reuptake causing more GABA to remain in the synaptic cleft, binding more to the GABA receptors, increasing the influx of chloride ions and, thus, decreasing neuronal firing.

Uses

It is used to treat

- Partial seizure
- Complex seizure

Topiramate

It is an anticonvulsant drug.

Mechanism of action

It inhibits the sodium channel and thus prevents the neuronal firing

It also facilitates the GABA inhibition of the neurons

Uses

Treat partial seizures i.e. simple partial seizure or complex partial seizures

Treat generalized tonic-clonic seizures

Prevent migraine headache

Side effects

Sedation

Mental dullness

Kidney stones

Weight loss

Valproic acid

It is an anticonvulsant drug

Mechanism of action

It inhibits the sodium channel activation and thus inhibits the neuronal firing

It also enhances the GABA inhibitory action

Uses

First line of agent in tonic clonic seizures

Partial seizures i.e. simple partial and complex partial seizures

Generalized tonic-clonic seizures, absence seizures

Myoclonic seizures

Side effects

GI distress i.e. nausea, vomiting

Neural tube defects i.e. spina bifida if taken by pregnant mothers in first trimester

Hepatotoxicity

Vigabatrine

It is an anticonvulsant drug

Mechanism of action

It irreversibly inhibit the GABA transaminase which is an enzyme that degrade GABA into succinate. The inhibition of this enzyme results in increased concentration of GABA at the synaptic cleft, stimulating more GABA receptors, increasing the chloride influx and decreasing the neuronal firing.

Uses

It is used to treat

- Simple partial seizure
- Complex partial seizure

Acetaminophen:

Acetaminophen:

It is often use as anti-pyretic and analgesic.

Mechanism of action:

Reversibly inhibits cyclooxygenase (COX) in CNS. COX actually forms prostaglandins and thromboxane A2. These prostaglandins stimulate pain in the body.

Metabolism of acetaminophen:

It is metabolized by two pathways:

Conjugation:

Conjugation produces 2 products:

1. Sulfate moiety.
2. Glucronide.

Cytochrome p450 pathway:

It produces N-acteyl-P-benzo-quinloneimine and this product is toxic to liver and causes hepatic necrosis. It is further metabolized by the glutathione to cysteine and mercaptopuric acid conjugate (non-toxic).

When person takes increased amount of the acetaminophen it causes hepatic necrosis.

Aspirin:

Aspirin:

Arachidonic acid pathway:

This is the most important pathway that regulates the process of inflammation in t body. Phospholipase A2 cleaves of the Arachidonic aid out of the membrane phospholipid bilayer present in the cell membrane.

Arachidonic acid can be converted into 2 pathways:

- Lipoxygenase pathway.
- Cyclooxygenase pathway.

Cyclooxygenase pathway:

Prostaglandins are produced in this pathway.

Prostacyclin:

- It decreases the platelets aggregation in the body.
- It decreases the vascular tone.
- It also decreases bronchial tone
- It decreases the uterine tone.

PGE2 andPGF2:

- Increases the uterine tone.
- Decreases the vascular tone.
- Decreases the bronchial tone.

Thromboxane A2:

- Increases the platelets aggregation.
- Increases the vascular tone.
- Increases the bronchial tone.

Lipoxygenase pathway:

Leukotrienes are produced in this pathway.

LTB4:

- Neutrophils chemotaxis.

LTC4 and LTD4:

They increase the bronchoconstriction.

Aspirin:

Aspirin is one of the NSAIDs (non-steroidal anti-inflammatory drugs)

Mechanism of action:

Aspirin inhibits cyclooxygenase by irreversibly inhibiting the cyclooxygenase 1 and 2 (COX1&2) enzymes.

Aspirin increase the bleeding time but no effect on prothrombin time (PT) and partial thromboplastin time (PTT).

Clinical uses:

- Low dose (<300mg)-it decreases the platelet aggregation.
- Intermediate dose (300-2400m)-acts as anti-pyretic.
- High dose (2400-4000mg)-acts as analgesia.

Toxicity:

- Gastric ulceration- GI bleeding
- Tinnitus (ringing in the ear)-it affects CN8.
- Acute renal failure/interstitial nephritis.
- Reye syndrome-children with viral infection develop this syndrome.

Metabolic derangement in aspirin over-dose:

- Respiratory alkalosis.
- Metabolic acidosis.

Gout drugs:

Gout:

Purines are converted into hypoxanthine and hypoxanthine is converted into xanthine by the action of xanthine oxidase then xanthine is converted to uric acid by the action of uric acid. Uric acid go through kidneys are converted to urate crystals. These crystal deposits in the joints and causes inflammation. Uric acid is also go through the nephrons and they reabsorbs in the tubules.

Gout drugs:

Drugs for chronic gout:

Allopurinol:

Mechanism of action:

Allopurinol is a xanthine oxidase inhibitor and then hypoxanthine is not converted to xanthine and uric acid cannot be formed.

Clinical use:

- Chronic gout.
- Lymphoma/leukemia (to prevent tumor-lysis syndrome).

Interaction:

Allopurinol causes increase in the azathioprine and 6-mercaptopurine concentration in the plasma.

Febuxostat:

Mechanism of action:

It inhibits xanthine oxidase enzyme.

Probenecid:

Mechanism of action:

It inhibits the reabsorption of uric acid in the proximal convoluted tubules in the kidneys.

Interactions:

It inhibits the secretion of the penicillin into the proximal convoluted tubules and causes disturbance in the excretion of the penicillin from the body.

Colchicine:

It binds and inhibits tubulin polymerization and in this way it disturbs the leukocyte chemotaxis.

Toxicity:

- Diarrhea.

Drugs for acute gout:

NSAIDs (non-steroidal anti-inflammatory drugs):

- Naproxen.
- Indomethacin.
- Ibuprofen.
- Ketorolac.

Mechanism of action:

They inhibit the cyclooxygenase and reduce the inflammation and pain.

Glucocorticoids:

Often use to treat inflammation in the body.

NSAIDs:

NSAIDs (non-steroidal anti-inflammatory drugs):

- Ibuprofen
- Naproxen
- Indomethacin.
- Ketorolac.
- Diclofenac.

Mechanism of action:

They reversibly inhibits cyclooxygenase enzyme 1&2.

Clinical uses:

- Pain control (analgesia).
- Anti-pyretic (reduces fever).
- Anti-infalammatory.
- Indomethacin is used to close patent ductus arteriosus (PDA).

Toxicity:

- Interstitial nephritis.
- Gastric ulceration.
- Renal ischemia-acute renal failure.

Cyclooxygenase 2 inhibitor:

- Celecoxib.

Mechanism of action:

It reversibly inhibits COX-2.

Clinical uses:

- Rheumatoid arthritis.
- Osteoarthritis.
- Patients having gastric ulcers.

Toxicity:

- Sulfa allergy cannot have this drug.
- Thrombosis.

Acetaminophen:

Mechanism of action:

Reversibly inhibits COX in central nervous system.

Clinical uses:

- Reduces pain.
- Anti-pyretic.
- To prevent Reye syndrome in children.

Toxicity:

When patient takes too much acetaminophen it causes hepatic necrosis. Liver function tests shows increase ALT/AST. Glutathione helps to prevent hepatic necrosis.

N-acetyl cysteine is the drug of choice in acetaminophen overdose.

Aminoglycosides

Aminoglycosides:

These are known as protein synthesis inhibitors.

Mechanism of action:

Aminoglycosides inhibits the:

- Formation of initiation complex and
- Protein formation by inhibiting translocation.

Aminoglycosides binds with the 3os ribosome and transfer RNA cannot bind the 30s ribosome.

Different aminoglycosides:

- Neomycin.
- Tobramycin.
- Amikacin.
- Gentamicin.
- Streptomycin.

Clinical use:

- E.coli.
- Pseudomonas.
- Klebsiella.
- Enterobacter.

Toxicity:

- Nephrotoxicity.
- Ototoxicity.

Aztreonam

Aztreonam:

Mechanism of action:

Aztreonam prevents the peptidoglycan cross linking by binding to the penicillin binding protein 3.

It is synergistic with aminoglycosides e.g. tobramycin, gentamicin, neomycin. If the patient has allergy to penicillin then you can give Aztreonam.

Clinical use:

- Gram negative rods.

Toxicity:

- Gastro-intestinal upset.

Carbapenem

Carbapenem:

Carbapenems are broad spectrum antibiotics.

Drug names:

- Imipenem/cilastatin.
- Meropenem.
- Ertapenem.
- Doripenem.

Cilastatin:

Cilastin inhibits renal dihydropeptidase 1 and prevents the conversion of imipenem to its active metabolite.

Clinical use:

- Gram positive cocci.
- Gram negative rods.
- Anaerobes.

Toxicity:

- Gastro-intestinal distress.
- CNS toxicity (seizures).
- Skin rash.

Chloramphenicol

Chloramphenicol:

Mechanism of action:

It binds to the peptidyl transferase at 50s ribosome subunit and prevents the bacterial growth and it is known as bacteriostatic.

Clinical use:

- Streptococcus pneumonia.
- Neisseria meningitis.
- Haemophilus influenza.

Toxicity:

- Anemia (aplastic anemia)-pancytopenia.
- Grey baby syndrome.

Resistance:

Resistance is due to transfer of the plasmid form one bacteria to another.

Clindamycin

Clindamycin:

Mechanism of action:

Clindamycin works by blocking peptide transfer at 50s ribosome subunit.

Clinical use:

- Bacteroides fragilis.
- Clostridium perfringes.
- Aspiration pneumonia/ lung abscess.
- Oral infections.

Toxicity:

Pseudomembranous colitis (closotridium difficle)- fever, diarrhea.

Fluoroquinolones

Fluoroquinolones:

Drug names:

- Ciprofloxacin.
- Norfloxacin.
- Gatifloxacin.
- Levofloxacin.
- Moxifloxacin.
- Nalidixic acid.

Mechanism of action:

Fluoroqinolones inhibits DNA gyrase (topoisomerase 2)/topoisomerase 4 and kills the bacteria by inhibiting its replication.

Clinical use:

- Gram negative rods (UTI)-pseudomonas.
- Neisseria.

Toxicity:

- Tendon rupture (>60yrs patients) on prednisone.
- Prolonged QT syndrome.

Resistance:

Resistance is due to:

- Chromosome encoded mutation in the DNA gyrase.
- Plasmid mediated.

Introduction to antimicrobials

Introduction to antimicrobials:

Terminologies:

Antibiotic selection:

Points that should be kept in mind before selecting antibiotic are:

1. We need to recognize the organism.
2. We need to know the safety of the drugs.
3. We need to know the site of infection.
4. Patient may have allergy to some antibiotic.

Classes of antibiotic:

1. Cell-wall inhibitors.
2. Protein synthesis inhibitors.
3. DNA gyrase inhibitors.
4. RNA inhibitors.
5. Cell membrane disruptors.

Bacteriostatic vs bactericidal:

1. Bacteriostatic: Bacteriostatic means to arrest the growth of the bacteria and then the body immune system can affect bacteria easily e.g. chloramphenicol, nitrofurantoin, clindamyicin, tetracyclin, erythromycin, trimethoprim, lincomycin.
2. Bactericidal: bactericidal drugs kill the bacteria in the body e.g. aminoglycosides, quinolones, cyclosporine, vancomycin, carbapenem, penicillin, cephalosporins.

Drug resistance:

It is the ability of the microorganism to withstand the drug that can potentially kill it.

Antimicrobial prophylaxis:

Prophylaxis is to prevent the other person to acquire the same infection in the close contacts as the case is having.

Empiric therapy:

It is the therapy that is initiated before the pathogen is detected in the body.

Antibiotics:

Cell-wall synthesis inhibitors:

- Beta lactams.
- Vancomycin.

Cell membrane disruptor:

- Amphotericin-B

DNA gyrase:

- Flouroquinolones.

DNA dependent RNA inhibitors:

- Rifampin.

Protein synthesis inhibitor (50s):

- Chloramphenicol.
- Macrolides.

Metabolic inhibitors:

- Sulphonamides
- Trimethoprim.

Macrolides

Macrolides:

Drug names:

- Azithromycin.
- Clarithromycin.
- Erythromycin.

Mechanism of action:

Macrolides binds to the 23s rRNA (50s) ribosome and prevents the translocation of the tRNA on the mRNA.

Clinical use:

- Pneumonia (atypical):
    1. Mycoplasma.
    2. Chalmydia.
    3. Legionella.
- Upper respiratory tract infections (URTIs).
- Sexually transmitted diseases (STDs).

Toxicity:

- Prolonged QT syndrome.
- Acute cholestatic hepatitis.
- Rash.
- Eosinophilia.

Interactions:

Macrolides increase the serum concentration of:

- Theophylline.
- Warfarin.

Resistance:

Resistance is due to methylation of the 23 rRNA.

Metronidazole

Metronidazole:

Mechanism of action:

Metronidazole forms toxic metabolites (nitroreductase) and disrupts the DNA in bacterial cell (bactericidal).

Clinical use:

- Giardia
- Entameoba hitolytica.
- Trichomonas.
- Gardenerella.
- Anaerobes.
- H.pylori.

Toxicity:

- Disulfiram reaction (nausea and vomiting on consumption of alcohol).
- Metallic taste.
- Hemolytic anemia (patient with G6PD deficiency).

Penicillin

Penicillin (beta lactams):

- Natural penicillin
- Anti-staphylococcus penicillin
- Anti-pseudomonal penicillin
- Extended spectrum.

Natural penicillin:

Drug names:

- Penicillin G (I/V).
- Penicillin V (PO).
- Penicillin G benzathine (I/M).

Bacterial cell-wall:

Bacterial cell is made of peptidoglycan. Bacteria contain penicillin binding proteins inside the cell these are involved in the synthesis of the cell wall. This cell wall has to be linked together by the help of the cross linking of the peptidoglycan in the cell wall of bacteria.

Mechanism of action:

Penicillin binds to the penicillin binding proteins and these protein won't be able to secrete peptidoglycan and it also inhibits transpeptidase and prevent the cross linking of the peptidoglycan in the cell wall of the bacteria and in this way bacterial cell disrupts.

Clinical uses:

1. Streptococcal pneumonia,
2. Streptococcal pyogenes,
3. Actinomyces,
4. Neisseria meningitis,
5. Treponema pallidum,
6. Syphilis,
7. Listeria monocytogenes.
8. Gram positive.

Adverse reactions:

- Hypersensitivity reaction (urticaria, hypotension, bronchoconstriction, fever, pruritis).
- Gastrointestinal symptoms.
- Hemolytic anemia.

Resistance:

Penicillin cannot affect the bacteria having beta lactamase.

Anti-staphylococcal penicillin:

- Methicillin.
- Naficillin.
- Oxacillin.
- Dicloxacillin.

Mechanism of action:

Its mechanism of action is as same as that of penicillin because it binds to penicillin binding proteins and prevents the peptidoglycan synthesis and cross linking of the peptidoglycan.

Clinical use:

- Staphylococcus aureus.

Toxicity:

- Hypersensitivity.
- Interstitial nephritis (methicillin).

Aminopenicillin:

- Amoxicillin.
- Ampicillin.

These drugs are beta lactamase sensitive.

Clinical use:

- Hemophilus influenza.
- E.coli/enterococci.
- Listeria monocytogenes.
- Proteus mirabilis.
- Salmonella.

Toxicity:

- Hypersensitivity reaction.
- Rash (jerisch herxheimer reaction).
- Pseudomembranous colitis (clostridium difficile).

Anti-pseudomonal penicillin:

- Ticarcillin.
- Carbenicillin.
- Pipracillin.

Beta lactamase inhibitors:

- Clavulanic acid.

- Salbactam.
- Tazobactam.

Mechanism of action:

Its mechanism of action is as same as that of penicillin but with beta lactamase inhibitors their action becomes stronger.

Clinical use:

- Pseudomonas.
- Gram negative rods.

Cephalosporins:

- 1st generation:
    1. Cephalexin.
    2. cefazolin
- 2nd generation:
    1. Cefoxitin.
    2. Cefaclor.
    3. Cefuroxime.
- 3rd generation:
    1. Ceftriaxone.
    2. Cefotaxime.
    3. Ceftazidime.
- 4th generation:
    1. Cefepime.

Mechanism of action:

Cephalosporin inhibits the bacterial cell wall synthesis.

Clinical use:

- 1st generation:
    1. Proteus mirabilis.
    2. E.coli.
    3. Klebsiella.
- 2nd generation:
    1. Gram positive cocci (haemophilus influenza.)
    2. Neiserria.
    3. Enterobacter aeruginosa.
    4. Proteus.
    5. E.coli.
    6. Klebsiella pneumonia.
    7. Serratia.
- 3rd generation:
    1. Meningitis.

2. Gonorrhea.
3. Pseudomonas.

- 4th generation:
  1. Pseudomonas.
  2. Gram positive.

Toxicity:

- Hypersensitivity.
- Vitamin K deficiency.
- Disulfiram like reaction (nausea, vomiting when alcohol is consumed).
- Increased toxicity with aminoglycosides.
- Low cross reactivity with penicillins.

Protein synthesis inhibitors

Proteins synthesis inhibitors:

Normal translocation on mRNA:

Different types of amino acids are added on the mRNA chain in the following sites:

A-site:

It is an amino acid site on which new amino acids add via tRNA.

P-site:

It is a peptidyl site on which peptide bond with adjacent amino acid is formed on the mRNA chain to form polypeptide chain.

E-site:

It is an exit site from which an empty tRNA exits from the ribosome bubble on mRNA.

Protein synthesis inhibitor drugs:

These are divided into two categories depending on the type of ribosome subunit which they inhibit:

50s inhibitors:

1. Linezolid.
2. Macrolides.
3. Clindamycin.
4. Chloramphenicol.

30s inhibitors:

1. Aminoglycosides.
2. Tetracyclines.

Sulfonamides

Sulfonamides:

Sulfonamide drugs:

- Sulfamethoxazole
- Sulfadiazines
- Sulfisoxazole.

Normal synthesis of DNA and RNA proteins:

Para-aminobenzoic acid (PABA) is mixed with the pteridine in the presence of enzyme dihydorpteroate synthase to form dihydropteroic acid which is converted into dihydrofolic acid. It is converted into tetrahydrofolic acid (THF) with the help of dihydrofolate reductase. Tetrahydor folic acid is converted to N5, N10-methylase THF which is converted into various metabolites:

- Purines.
- Thymidine.
- Methioinine.

Mechanism of action:

- Sulfonamides inhibit dihydropteroate synthase.

Clinical use:

- Gram positive.
- Gram negative.
- Nocardia.
- Chlamydia.
- E.coli (UTIs).
- Toxoplasma gondii.

Toxicity:

- Hemolytic anemia in G6PD deficient patients.
- Tubulo-interstitial nephritis.
- Photosensitivity.
- Kernicterus (Infants).

Resistance:

Resistance is due to bacterial mutation.

Tetracycline

Tetracyclines:

Tetracyclines are protein synthesis inhibitors.

Drug names:

- Tetracycline.
- Doxycycline.
- Demeclocycline.
- Minocycline.

Mechanism of action:

Tetracyclines bind to 30s ribosome subunit and prevents the aminoacyl tRNA from binding to A site.

Doxycycline is good for renal failure patients because it is excreted in the feces.

Cautions:

- Anacids.
- Iron pigmented drugs.
- Milk.

Clinical use:

- Borelia burgdorferi (lyme disease) -DOC is doxycycline.
- Mycoplasma pneumonia (atypical pneumonia)-doxycycline.
- Chlamydia infection (STD)-doxycycline.
- Rickettsia.

Toxicity:

- Teeth discoloration.
- Photosensitivity (sun burn).
- Inhibits bone growth in children.

Demeclocycline is an ADH antagonist and thus acts as a diuretic.

Trimethoprim

Trimethoprim:

Mechanism of action:

Trimethoprim inhibits the dihydrofolate reductase enzyme involved in the conversion of dihydrofolic acid tetrahydro folic acid.

Clinical use:

- Simple urinary tract infections (UTIs).
- Shigella.
- Salmonella.
- Pneumocystic jirovecii pneumonia.

Toxicity:

- Megalobastic anemia (MCV>100fl).
- Leukopenia- granulocytopenia.

To prevent this toxicity folinic acid (leucovorin) is given.

vancomycin

Vancomycin:

Mechanism of action:

Binds to D-alanyl-D alanine cell wall precursors and inhibits peptidoglycan polymerization.

Clinical use:

- Methicillin resistant staphylococcus aureus (MRSA).
- Pseudomembranous colitis (clostridium difficile).

Toxicity:

- Nephrotoxicity.
- Ototoxicity.
- Thrombophlebitis.
- Red man syndrome- “diffuse flushing”.

Anti-histamine (Diphenhydramine) is the drug of choice for “red man syndrome”.