India Connecting Continents (ICC)

Study materials for FMGE

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PHARMACOLOGY

* ROA → Route of Administration (Medicine is given by this)
* MC ROA → Oral
* ROA → Intestine → Plasma → Absorption → Distribution (to various parts of body) → then drug binds to target → then action → metabolized → end products of drug which are inactive metabolites : Elimination

ANS

(Autonomic Nervous System)

* Absorption → Distribution → Metabolism → Elimination

⇓

Pharmacokinetics

* Target → Action of drug

⇓

Pharmacodynamics

* ANS contains autonomic nerves which supplies smooth muscles & cardiac muscle (involuntary muscles)

CNS
↓ (controls)
PNS
→ Sensory nerves
→ Motor nerve

CNS
↓
PNS
→ Sensory (Na^+)
→ Viscera
→ Somatic
→ Motor
→ Viscera
→ Somatic

Sensory (viscera + somatic) → Na^+ (touch, pain, prick) → Na^+ enters the nerve → sensation from periphery to CNS is carried by Na^+ → Nerves - Sensory nerve System - Sensory nervous system

ACh - Acetyl choline
NAdr - Nor Adrenaline
NEpi - Nor Epinephrine
(R) - Receptor

Motor (neurotransmitter)
→ Viscera (Involuntary muscles) → Smooth & cardiac muscles → Autonomic nervous system → NT: ACh / NAdr or NEpi
NAdr R : α & β
ACh R : M & N_N
(M: muscarinic, N_N - Nicotinic nerve type)

→ Somatic (Voluntary) → Somatic nervous system → NT : ACh
Receptor : N_M (Nicotinic - muscle type)

* Medicine blocks CNS → General Anesthetics

* MOA : Mechanism of Action (Pharmacodynamics)

* MOA of General Anesthetics
↓
Binds to $GABA_A$ receptor
↓
Stimulates $GABA_A$ receptor which is an inhibitory pathway
↓
inhibits CNS (so no sensation felt)

* Medicine blocks sensory NS → Local Anesthetics
↓
MOA / PD : Binds to Na^+ channel & blocks it → so no Na^+ release.

* Local Anesthetics ⇒ ends with "-caine"
eg: Lidocaine
Cocaine (but not used)

* Medicines blocks somatic NS (blocks voluntary muscle - Skeletal muscle) → Skeletal muscle relaxant (used during surgery)
↓
MOA / PD : Binds to N_M receptor
↓
Ach can't binds to Nm
↓
No muscle movement.

* Skeletal muscle relaxant drugs ends with "-curium"
eg: Mivacurium

Medicines acts on ANS

ANS (controlled by hypothalamus)

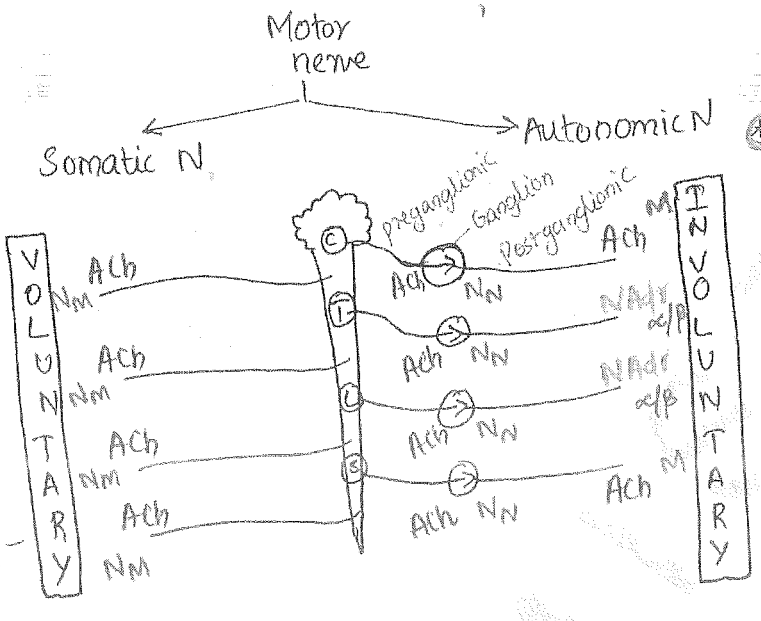
Sympathetic NS	Parasym. NS
* Stressful stimulus	* Non-stressful
* Postero lateral nucleus of hypothalamus (PLUS)	* Antero medial nucleus of HT (cAMP)
* Thoraco lumbar outflow ($T_1 - L_2$)	* Craniosacral outflow ↓ C → 3, 7, 9, 10 S → $S_2 - S_4$
* NT → NAdr / NEpi R → α & β (R - Receptor)	* NT : ACh R : M & N_N
* Adrenergic system.	* Cholinergic system

Motor Nerves

Somatic Nerves
↓
Muscles of head and neck
↓
supplies voluntary muscle

Autonomic Nerve
↓
involuntary muscles
↓
Smooth muscle

* Somatic nerves → ACh → N_M receptors → voluntary muscle
* Autonomic nerves → C, T, L, S → nerves from them ends up in ganglion → from ganglion to periphery → T&L : NAdr – α&β → C&S : Ach – M, N_N



* All type of pre-ganglionic nerves release ACh in ganglion → the receptor here is N_N
* All somatic nerves, all preganglionic nerves, all post-ganglionic parasym. nerves are cholinergic (releases ACh)

Somatic → R: N_M
Pre-ganglionic → R: N_N
Post. G – PS → R: N_N, M

(R: Receptor)

Cholinergic

* All somatic nerves – N_M
* All pre-ganglionic nerves – N_N
  - sym
  - parasym.
* All type of post. ganglionic parasym. – M
* Post ganglionic sympathetic nerve → to sweat glands → ACh ; M (R)

((R)-receptor, M-muscarinic)

Adrenergic

* All post ganglionic sympathetic N
* NAdr
* (R) : α & β

3 exceptions

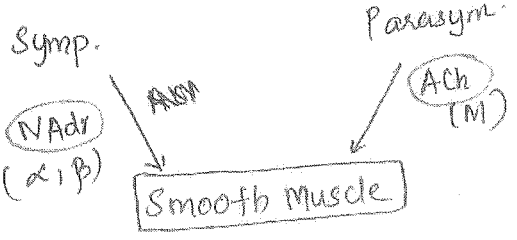
(1) Sweat gland ACh → M (sweating)
(2) Renal & mesenteric blood vessels Dopamine ((R) is D_1) (vasodilation)
(3) Adrenal medulla Adr >> NAdr

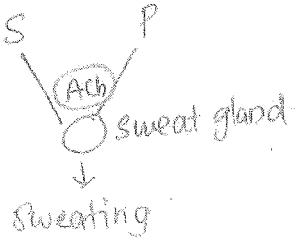
---

* Sweat gland is associated with both sympathetic & parasympathetic nervous system.

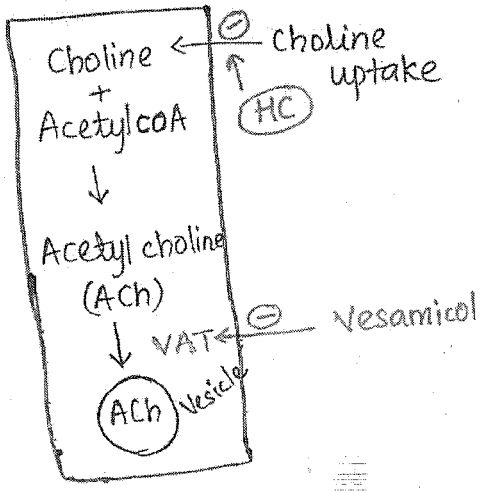
(If no sweating → hyperthermia)

* Dopamine → D_1 → vasodilation
* Adrenal medulla is the only one source of Epinephrine.

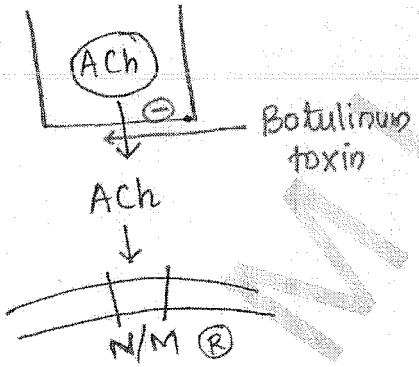




Cholinergic nerve



* ACh enter in to vesicle with the help of VAT (transporter protein)
↓
Vesicular ACh Transporter.



Somatic NS → N_M

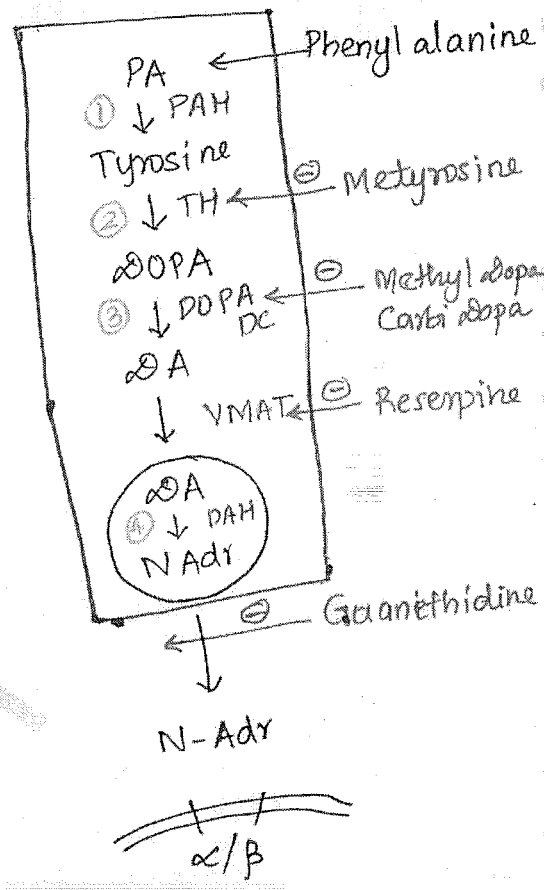
~~Parasym~~ NS → N_N
ANS - Preganglionic

⊛ Choline uptake blockers :-
- Hemicholinium.

⊛ Blocker of VAT
- Vesamicol

⊛ Blocker of ACh release
- Botulinum toxin.

Adrenergic nerve



* VMAT : Vesicular mono amine transporter

MCQ
✓ ① → Phenyl alanine hydroxylase
✓ ② → Tyrosine hydroxylase
✓ ③ → DOPA decarboxylase
✓ ④ → Dopamine hydroxylase.

✓* Except dopamine hydroxylase all others present outside vesicle

✓* Not hydroxylase → DOPA decarbox converts DOPA to DA.

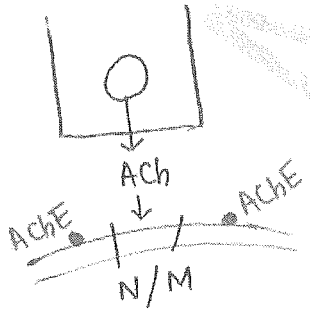
* Blocker of TH : Metyrosine
↓
Given for adrenal cancer. (Pheochromocytoma)

* Blocker of αDOPA decarboxylase
  - Methyl αDOPA
  - Carbi αDOPA
* Blocker of VMAT is:
  Reserpine
* Blocker of release of NAd
  Guanethidine

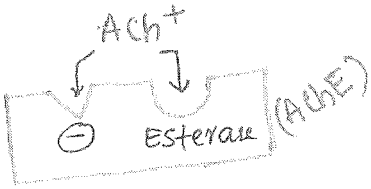
ANS

* ANS has autonomic nerves which supplies involuntary muscles (smooth muscle, cardiac muscle)
* 2 types → Sympathetic & Parasympathetic
* ACh & NAdr

Metabolism of ACh

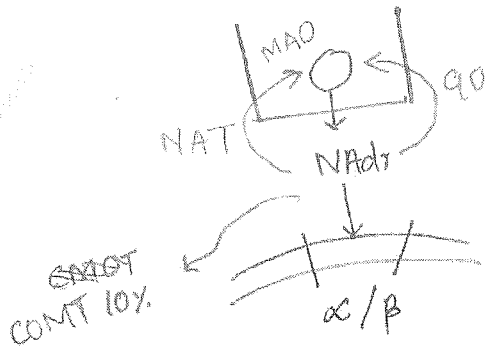


* ACh is metabolized by Acetyl choline esterase (AChE)
* AChE is present on post synaptic membrane (surface)
* $t_{1/2}$ of ACh → 1 second.
* ACh is released in to synaptic cleft
* most one enzyme have 1 site
* But in AChE → 2 site → Anionic site (-ve) & Esteric site → Ach has +ve charge



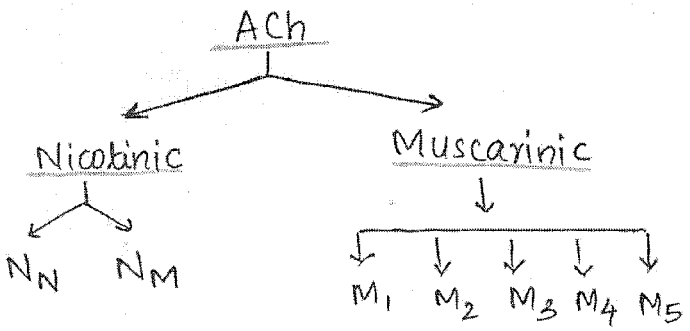
* ACh attaches to anionic site → Attachment
* Hydrolysed by estrase → Hydrolysis (metabolism)

Metabolism of NAdr



* Around 90% of released NAdr is taken up (re-uptake)
  ↓
  By NAT (Noradrenaline transporter)
  ↓
  Then metabolized by MAO (Mono Amine Oxidase)
* 10% NAdr → comes out of synaptic cleft → taken up by tissues in body, metabolised by COMT.
* $t_{1/2}$ NAdr → 3-4 minutes.
* COMT: Catechol (cholamine) ortho methyl transferase

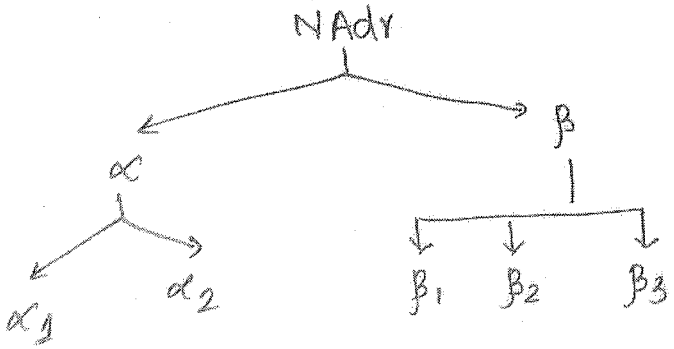
Receptors of ACh



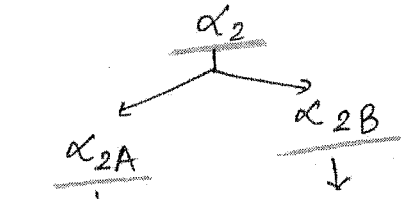
* N_M → Part of somatic NS (voluntary)
* N_N → Autonomic NS (Ganglion)
* M_4 & M_5 → CNS
* M_3 → Over all smooth muscles & glands in body (except cardiac)
  (When M_3 stimulated, smooth muscles & gland depolarises)
* M_2 → Cardiac cells
* M_1 → Acid secreting cells of stomach.

Here M_1 & M_3 is present
$M_3 >>> M_1$ here
(M_3 present in all)

Receptors of Nor Adrenaline



* β_3 → Adipose tissue
* β_2 → Present over all muscles
  (when β_2 stimulated, releases cAMP – secondary messenger)
  ↓
  smooth muscles will be relaxed but cardiac & skeletal muscle will get contracted.
* β_1 → Cardiac cells, JG cells of Kidney (secretes Renin), Ciliary body of eye (synthesis of aqueous humour).
  (CCC)
* α_1 ⇒ Over blood vessels, Prostate, Eyes (radial muscle of iris), Sphincter
  (PROBES)
* α_2 ⇒ Two types: α_{2A} & α_{2B}



α_{2A}
- CNS
- Presynaptic
- Inhibitory
- All centres of CNS.

α_{2B}
- PNS
- Post synaptic
- Excitatory.
- Blood vessels of PNS.
  (Vaso constriction)

* α_2A present mainly in CNS
* Also in PNS → platelets, JG cells, β-cells.
  (CNS >>> PNS)

Actions of ACh & NAdr

* Parasym → Accomodation & Miasis (M_3)
* Sympa → cycloplegia (β_2) & mydriasis (α_1)

1) Eyes:

Eyes
- Extra ocular (4 rectus & LPS) → Voluntary, somatic NS → Receptor: N_M
- Intra ocular → involuntary → Lens, Iris

Lens (ciliary muscle)
- Sympathetic → β_2 → muscle relaxes → Loss of accomad^n known as cycloplegia.
- Parasympathetic → (R) M_3 → ciliary muscle contracted → Accomodation (for near vision)

Iris
- Circular muscles fibers → Parasympathetic → M_3 → Miosis (Pupil constricts) (sphincter pupillae muscle)
- Radial muscles fibers → Sympathetic → α_1 → Mydriasis (pupil dilates) (dilator pupillae)

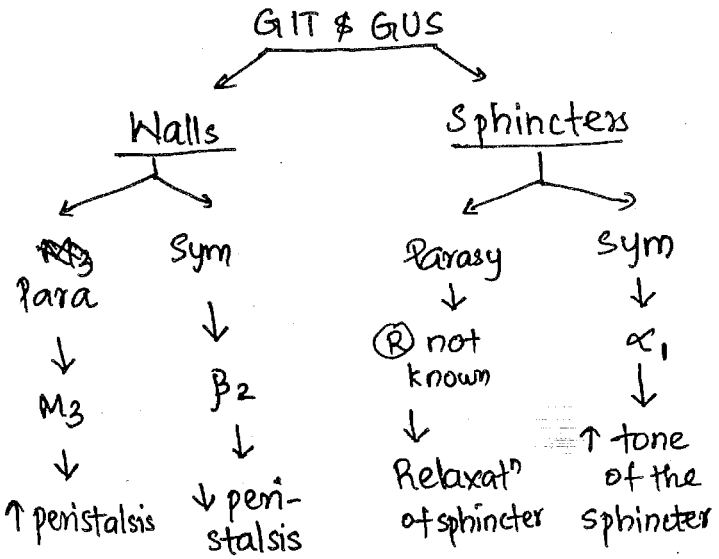
2) Bronchioles

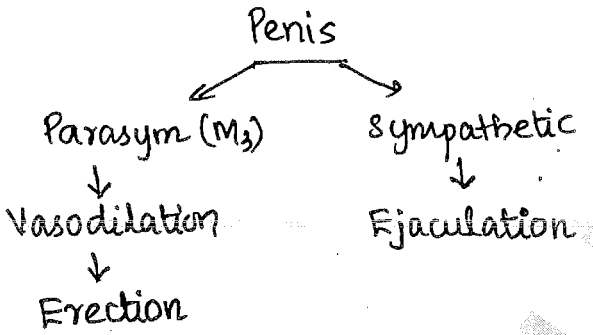
- Parasym → M_3 → Broncho constriction
- Sym → β_2 → Broncho dilation (more O_2 intake)

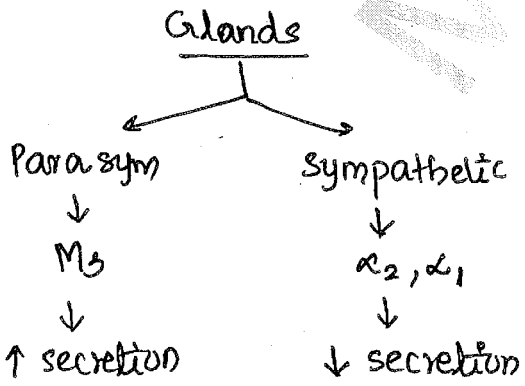
3) CVS

CVS
- Heart
  - Parasym → M_2 → ↓ HR → ~~Brady~~ -ve stimulation
  - Sym → β_1, β_2 → ↑ HR → Tachycardia
- Blood vessels
  - Para → Vasodilat^n (indirect) → due to release of nitric oxide
  - Symp → Vaso constrict^n → (R): α_1, α_2 B

3) GIT & GUS (Genito-urinary system)

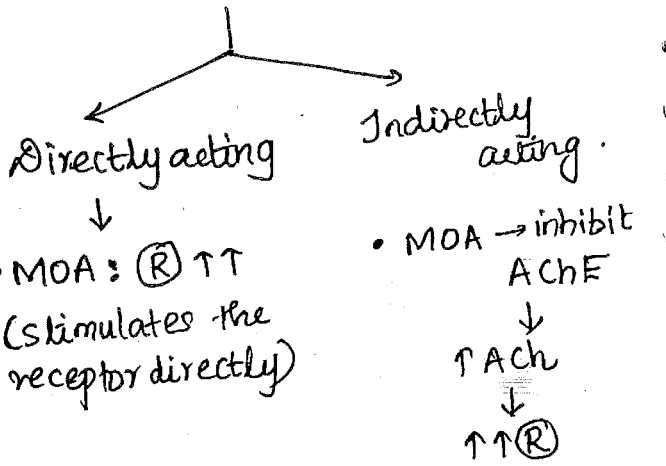






* ACh → M_3 → release of NO → vasodilation → erection.

Cholinergic Drugs (Parasympathomimetics)



Directly acting Parasympathomimetics

① * ACh → acts on N, M,
* Duration of action is 1 sec ($t_{1/2}$ = 1 sec) (short $t_{1/2}$)
* Can act on both N & M (non specific)
* N_N is maximum in CNS

② ACh + Methyl choline → Methacholine
* Acts only on R M
* But $t_{1/2}$ very short (1sec)

③ ACh + Carbomoyl → Carbachol
* Present in both N & M
* $t_{1/2}$ increases (lock & key model of enzyme activity → when both combines, shape of ACh changes → more effective)

(4) ACh + Methylcholine + Carbomoyl (Bethanechol)

* Only act on M (muscarinic) (so specific)
* $t_{1/2}$ increases (long acting)

⇒ All these medicine ~~acts~~ have action on M

↓

All acts on M_3 mainly except Methacholine ($M_2 > M_3$) MCQ

⇒ Bethanecol is the medicine which is used clinically.

↓

Mainly acts on bladder (M_3)

• Bladder muscle (detrussor) Contracts → Urination

↓

used in Rx of retention of urine in conditions like:

(i) BPH (Benign Prostatic Hyperplasia)

(ii) Post operative (start Ringer Lactate – then can pass urine & motion)

(iii) Hypotonic bladder (Bladder Atony)

↓

(Bed wetting)

↓

DOC: Bethanecol (best Rx)

(5) Pilocarpine (Plants / Trees) (k/a Alkaloids)

* Alkaloids are medicines which are obtained directly from plants / trees.
* Used in Eye drop (Acts on M_3)
* M_3 → Miosis → widening of iridocorneal angle → ↑↑ trabecular drainage → IOP ↓ → so used in Rx. of Glaucoma (in closed angle Glaucoma)
* Also used in the ~~oral~~ form of tablets
* Tablet → M_3 ↑ → ↑ gland secretion → used for Rx. of Sjogren's syndrome (here Ab formed against glands of body – dry eye, dry mouth, dry skin, hyperthermia (no sweating), impaired digestion)

Indirectly Acting Parasympathomimetics

* MOA: Inhibit AChE → ↑ ACh → (R) ↑↑

Enzyme inhibitor

- Reversible → electrostatic bond with enzyme (Weak bond) (Block releases after some time as weak bond)
- Irreversible → covalent bond (strong bond) (remain block forever)

* Irreversible → ~~toxins~~ poisonous for the body.
* Clinically used is reversible.

Irreversible blocker

1) Organophosphates } Insecticides, Pesticides.
2) Carbamates }

* Organo PO_4 blocks esterase in AChE → ACh ↑ → results in cholinergic poisoning
* Carbamates → forms covalent bond with anionic & esterase side of AchE → ACh ↑ → cholinergic poisoning.
* Causes miosis, lacrimation, drooling of saliva, ↑ sweating k/a hyperhydrosis, bradycardia, hypotension, bronchoconstriction - wheezing, diarrhea, incontenence of urine, electrolyte imbalance which leads to seizures.
* TOC (Treatment of choice):

MCQ

Anticholinergic → Atropine (blocker of muscarinic receptor)

↓

i.v Atropine

* Oximes are also used here
* Oximes are used only for organophosphate poisoning. (not carbamates)

eg: Pralidoxime, Diacetyl Monoxime, Obidoxime.

* Oximes → + charge on ~~substance~~ surface → $[OP]^-$ goes to esterase → ot to anionic site (-) → ~~after some~~ ot & OP^-, forms bond. So OP^- does not block AChE and ACh ↓.
* So oximes should be given before covalent bond formation b/w poison & AChE.
* This process of covalent bond formation is k/a Ageing.
* Thus Oximes are useful in organo PO_4 poisoning before Ageing

MCQ

* OP & C poisoning → Cholinergic irreversible blocker.
* Carbamate poisoning → cant use oximes → as carbamate occupies both sites of AchE

Reversible inhibitor/ blocker

Reversible

- Tertiary (lipid soluble) → no charge → lipid soluble, so can pass cell membrane
- Quaternary (lipid insoluble / H_2O soluble) → charged compound (polar compound)

Tertiary
↓
cross CM
cross BBB
↓
metabolized by liver
↓
① Physostigmine
- Given i.v
- DOC for anticholinergic poisoning (Atropine poisoning)

Quaternary
↓
can't cross BBB
↓
eliminated through kidney

Tertiary

1) Physostigmine
- Given i.v
- DOC for anticholinergic poisoning (Atropine poisoning)
- Also used in Belladona poisoning, Datura poisoning.

2) Donepezil, Rivastigmine, Galantamine.
- Enter CNS & ↑ ACh in CNS → ↑ N_N → ↑ memory.
- Best – RxOC: Dementia (Alzheimer's disease)
- DOC – Donepezil for

Quatenary

1) Pyridostigmine (slow acting)
- DOC: Myasthenia gravis (Abs against N_M receptors on skeletal muscle)
(MC involved – eye)
(unable to move eye, open eye)
* Symptomatic relief will be there for Myasthenia gravis
- MOA: Inhibits AChE

2) Neostigmine:
- Fast acting drug
- DOC – Acute muscle weakness
↓
seen in immediately block
① after Cobra bite (NMJ ⊗)
↓
TOC: Anti snake venom + Neostigmine.

② • Also used in post. operative retention of urine and paralytic ileus after surgery

③ • Post operative reversal of skeletal muscle relaxation
DOC: Neostigmine

④ • 2nd DOC for Myasthenia gravis → Neostigmine

3) Edrophonium
- Shortest acting
- Given i.v
- Used in diagnosis of Myasthenia gravis.
↓
with the help of Tensilon test
↓
Muscle weakness
can be due to
N_M ⊗
Over stimulation of N_M
(↓ down regulation)

Edrophonium (2ml, i.v)
↓
↑ ACh
improves
worsens

* If symptom improved → give 8 mg i.v Edrophonium → ~~again~~ give → further improvement → So can confirm diagnoses of Myasthenia gravis

↓

MCQ

- Total dose : 10 mg (2+8)
- Initial dose : 2 mg
- small initial dose is given to rule out cholinergic crisis
- High dose is given to confirm diagnosis.

Cholinergic drugs (Parasympathomimetics)

↓

Directly acting

1) ACh
2) Methacholine
3) Carbachol
4) Bethanechol
5) Pilocarpine

Indirectly acting

↓

Reversible

↓

Tertiary

1) Physostigmine
2) Donepezil, Rivastigmine, Galantamine

Quaternary

1) Pyridostigmine
2) Neostigmine
3) Edrophonium.

Irreversible

1) Organo PO_4
2) Carbamate

Parasympatholytics

(Anticholinergics)

- Peripheral nerve blockers
- Nicotinic receptor blockers
- Muscarinic receptor blockers.

Peripheral nerve blockers:

- Hemicholinium (blocks uptake of choline)
- Vesamicol (inhibit VAT)
- Both are used in animal experiment
- Botulinum toxin (inhibit ACh release) used clinically.

* Botulinum toxin

* From Clostridium bacteria.
* Used clinically → Type A > B toxin
* Dose of drug calculated in units (100-300 units)
* More t½ (2-3 months)
* So long acting.
* Given by local route (not given by i.v / oral) → local injection.
* ~~Used for~~ muscle relaxation causes.
* Used in spasticity, Blepharo spasm (spasm of eyelid muscle), Strabismus (squint), Wrinkles over face

Nicotine blockers

- N_N ⊗
- N_M ⊗

N_M blockers

- Skeletal muscle relaxant (ends by -curium)
- Reversed by giving Neostigmine

N_N blockers

- Ganglion blockers
  - Hexamethonium
  - Trimethaphan
- Both sym. & para. ganglion blocks. But sym. >> parasym
- Sympathetic ganglion block
  ↓
  ↓ BP, so used to Rx HTN
  (HTN_N)

Muscarinic ® blockers

- Nonspecific
  ↓
  (blocks M_1-M_5 all)
- Specific

Nonspecific M⊗

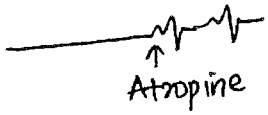
1) Atropine:
   - Belladona plant
2) Hyoscine (Scopolamine)
   - Hyoscine Niger plant

Atropine

* Indications are:

1) DOC for OPO_4 & Carbamate poisoning. (cholinergic poisoning)

2) Sinus bradycardia / Heartblock / Cardiac arrest (Vasovagal attack)

- ECG ⇒ 

- M_2 ⊗ → blocks parasym. effect → sympathetic ↑ → β_1 ↑ → HR ↑
- During CPR, use Atropine to ↑ HR.

(Vagus → CN 10 → parasym.)

3) Non infective diarrhea.

- Atropine blocks M_3 → ↓ peristalsis [M_3⊗]

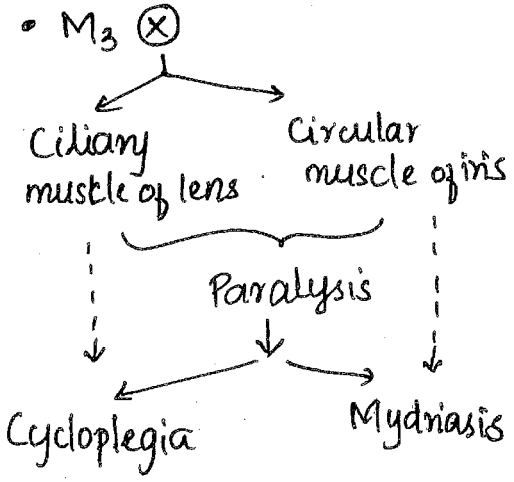
(⊗ : Blocks)

4) Pre-anesthetic medication:

- Before anesthesia → M_3 ⊗ → ↓ glandular secretions → helpful during surgery.

5) Eyedrops / Eye ointment:

- M_3 ⊗



- Mydriasis → useful in retinoscopy, refractive error, anterior uveitis (prevents iris sticks to lens - synechiae formation)
- Most effective Mydriatic, most effecient (7 days)

↓

Atropine

Hyoscine

* DOC for motion sickness (when excess movement → ↑ vestibule activity → ↑ Ach (M) release → Nausea, vomiting, Vertigo.
* It blocks M (receptor)
* Used as tablet, skin patch - posterior auricular skin because minimum skin thickness, (so ↑ absor) also near to vestibule.
* Given before journey starts
* Motion sickness also k/a
  - = Flight → Air sickness
  - = Ship → Sea sickness
* Used in GIT spasm & GUS spasm (Genito Urinary Spasm)
* Relax GIT & GUS, also used in colicky pain (ureter stone), non specific abdominal pain, dysmenorrhea.

Toxicity / s/e

* Anticholinergic poisoning
* dry eyes, dry mouth, hypohydrosis (↓ sweating), hyperthermia, constipation, retension of urine, dilated & fixed pupil, ↑ HR, psychotic symptoms in CNS., BP almost remains normal.
* DOC – Physostigmine (i.v) (for both Atropine & Hyoscine poisoning)

C/I of Atropine & Hyoscine

* Closed Angle Glaucoma (mydriasis → angle narrows → ↑ IOP → aggrevates glaucoma)
* BPH – Retension of urine (it further causes retension of urine)

Specific Muscaranic blockers

M_1 blocker: → ~~Pirenzipine~~, ~~Telenzipine~~.

- CNS → ⊗ Receptors in substantia nigra → Rx. Tremors, Rx. Parkinson's disease → Benzhexol, Benztropine.
- PNS → ↓ acid secretion in GIT → so used in Rx of peptic ulcer disease → Pirenzipine, Telenzipine.

* Parkinson's disease medicines used
  - Benzhexol (Trihexyphenidine)
  - Benztropine.

⇒ No M_2 blockers.

M_3 blockers:

1) Eyedrops → M_3 ⊗ → Mydriasis with cycloplegia it causes. → Same indication as Atropine
   - Tropicamide
   - Cyclopentolate
   - Homatropine
2) Inhalational → Bronchodilation → Rx. Bronchial asthma, COPD
   - Ipratropium bromide
   - Tiotropium bromide (long $t_{1/2}$)
3) GIT & GUS → Used as spasmolytic (same as Atropine)
   - Dicyclomine
4) Glands → ⊗ secretion → used as pre-anesthetic medication.
   - Glycopyrrolate (highly lipid insoluble ← so don't act on CNS) — less s/e (But Atropine can act on CNS)
   - Glycopyrrolate better than Atropine.

5) Acts on bladder → Relax detrussor muscle → Rx. Overactive bladder (urge incontinence)
- Oxybutirin (DOC)
- Tolterodine
- Darifenacin
- Solifenacin

Catecholamines

- Natural (endogenous)
  1) Dopamine
  2) Nor Adrenaline
  3) Adrenaline
- Synthetic (exogenous)
  1) Dobutamine
  2) Isoprenaline
  3) Fenoldopam

Sympathomimetics (Adrenergic)

* Thoracolumbar, T_1 to L_2, NT is mainly NAdr or NEpi.
* Stressful condition.
* (R) → α (2), β (3)

* $t_{1/2}$ of catecholamine 3-4 min
* Metabolized by MAO enzyme & COMT enzyme

* Used always - i.v
* Useful for acute emergencies
* Not used in OPD
* All are lipid ~~sol~~ insoluble → cannot cross BBB → cannot act on CNS

(Depression – deficiency of serotonin, noradrenaline)

- Sympathomimetics
  - Directly acting → R↑↑
  - Indirectly acting → ↑ NAdr → R↑
  - Mixed action → Direct + Indirect action in body

- Directly acting
  - Catecholamines
  - Non-catecholamine

Dopamine

* Acts of (R) D_1, α_1, β_1
* Dopamine 1-2 µg/kg/min → acts on D_1 (R) in renal & mesenteric artery → vasodilation in kidney & mesentry → GFR ↑, ↓ BP (blood directed towards GIT)

* Dopamine → 2-10 µg/kg/min → acts on D_1 & β_1 → Vasodilation → stimulates heart.

Heart

- Muscle (Atrial & Ventricular) → ↑ force of contract^n (Inotropic)
  - Dopamine has more affinity for muscle.
- Nodal tissue (SAN, AVN, Purkinje) → ↑ SAN, ↑ HR (Chronotropic)
  - AVN ↑, conduct^n velocity ↑↑ (Dromotropic)
  - Dopamine has less affinity for nodal tissue.

⇒ Muscle >>> Nodal tissue

* So used as Inotropic drug (↑ cardiac output)

* Dopamine → >10 µg/kg/min → acts on D_1, β_1 & α_1 (R) →
  - β_1 → Inotropic effect
  - α_1 → Vasoconstriction
  - D_1 → Vasodilation

* α_1 predominant over D_1 always ie, Vasoconstriction occurs

* Rx → Cardiogenic shock (condition with very less cardiac output - he can't survive)
  - (N) ejection fraction > 60%
  - Cardiogenic shock » < 40%

* Cardiogenic shock → less CO → blood supply to organs ↓ → kidney - GFR ↓ → BP ↓ (sometimes BP < 70 mmHg)
  - Cardiogenic shock with oliguria
  - Cardiogenic shock with low BP

⇒ Give Dopamine : 2-10 µg/kg/min (want β_1 ↑ & D_1 ↑) in C. shock ~ oliguria

⇒ Give Dopamine > 10 µg/kg/min in C. shock ~ low BP.

* S/e of Dopamine:
  - Tacchycardia (↑ HR)
  - Arrythmia (↑ cond^n velocity)

Adrenaline

* Acts on all receptors → stimulate all (R)

* α_1 ↑↑ → Vasoconstriction

* α_2 → α_2A → CNS → (X) can't cross BBB
  → α_2B → PNS blood vessel → constriction.

* β_1 ↑↑ → stimulate heart (~~SA~~) → ↑ chronotropic & dromotropic effects, no inotropic action → (Nodal tissue >>> Muscle)

* $\beta_2 \uparrow\uparrow$ → vasodilation, broncho-dilation.
* $\beta_3 \uparrow\uparrow$ → lipolysis.
* Adrenaline / Epinephrine
* Indications:
  1) Heart block / cardiac arrest
     • (Used during CPR) (DOC)
     • Dose 1 ml or 1 mg, i.v
     ≠ Not used in concentrated form → dilute in 1000 ml Normal saline → from this give 1ml (1:1000)
  2) DOC for anaphylactic shock (Severe hypersensitivity reactions) → Type I
     • Type I HSR → IgE ↑↑ → acts on mast cells → releases histamine → acts on H_1 ® → vasodilatn → ↓ BP → hypotensive shock immediately (within 1 min) → bronchoconstriction → respiratory arrest

[Adrenaline alone can act on α_1 & β_2. α_1 → ↑ BP, β_2 → Broncho dilation]

[Histamine $\xrightarrow{H_1}$ Hypotension, bronchoconstriction]

MCQ

[Adrenaline & Histamine are physiological antagonists]

* Dose: 0.5 ml or 0.5 mg
* ROA: i.m (i.v causes arrythmia)
  • Concentration = 1:1000 NS
  ↓
  If ROA : i.v
  concen = 1:10,000 NS

Anaphylatic shock
- DOC is Adrenaline (unstable patient)
- Can give Antihistanimics if patient is stable (iv/oral)
- Then Hydrocortisone (steroid)

3) Used in Status Asthmaticus (Acute severe asthma)
   • $\beta_2 \uparrow\uparrow$ → bronchodilation
4) Along with local anesthetics
   • As Adrenaline + Lignocaine
   • All local anesthetics are vasodilators
   • Adrenaline causes vasoconstric? → so drug lignocaine wont absorp in to systemic circulatn → so lignocaine present in that area for longer time → improves action)

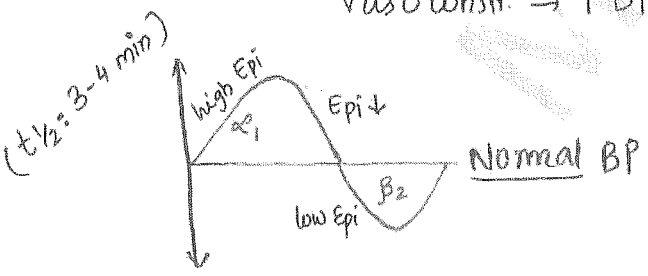
* S/e of Adrenaline:
  • ↑HR (Tachycardia)
  • Arrythmia
  • HTN

Nor-Adrenaline

* Non agonist of β_2.
* Acts on all receptors except β_2.
* α_1 → vasoconstriction
* α_2 → vasoconstriction
* β_1 ↑ → ↑ Ionotropic > ↑ chrono, ↑ dromo
* β_3 → Lipolysis
* DOC for hypotensive shock
* DOC for acute hypotension
* For Rx. cardiogenic shock.
* S/e ⇒ ↑ HR, Arrythmia, HTN

Animal experiments

* Adrenaline (Epinephrine) → Low dose → β_2 – Vasodil^n ↓BP
  → ↑↑ dose → $\beta_2 < \alpha_1$ → Vasoconstr. → ↑ BP



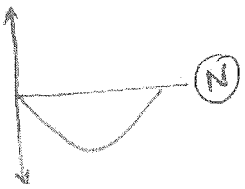
⇓

Known as Biphasic response on Adrenaline.

⇒ 1942, Henry Dale done an experiment.

Sym → α_1 → ↑ BP

* First he gave α blocker & then injected Adrenaline.
  (no α, so only ↓ BP experiences)



* Vasomotor Reversal of Dale
  (he was not aware of β_2)
  ↓
  1st α ⊗ → Adr → Vasodilat^n → ↓ BP
  he found out this.
  ↓
  This lead to discovery of β_2 ®

Synthetic catecholamines

* Exogenous catecholamine

1) Dobutamine:
   * MOA → β_1 ↑↑ agonist
   * Acts on heart (acts on muscle → ↑ ionotropic effect)
     (I ↑ > chrono, dromo. ↑)
   * Most specific inotropic agent
   * Not preffered when
     (i) Cardiogenic shock with oliguria (β1, D1)
     Dopamine
     (ii) Cardiogenic shock with low BP. (β1, α1)
     Dopamine (high dose)
     NorAdrenaline.

B.dil^n → Broncho dilation

2) Isoprenaline

* MOA: $\beta_1, \beta_2, \beta_3$ ↑
  - β_1 ↑ Iono
  - β_2 B.dil^n
  - Rx. Cardiogenic shock
  - Rx. status asthmaticus
* S/e: ↓ BP, ↑ HR, Arrythmia

3) Fenoldopam

* MOA: Only act on α_1
* ↑ GFR, ↓ BP
  (α_1 → vasodilation in kidney → ↑ GFR, → vasodilat^n in mesentry so ↓ BP.
* Rx: Hypertensive crisis

Non-catecholamine

* MOA – α_1 ↑↑

1) Phenylephrine

* Given as eye drop → contracts radial muscle of eye → mydriasis
* mcq. Here Mydriasis without cycloplegia.

2) Naphazoline, Oxymetazoline, Xylometazoline

* Naphazoline – Eye drop
* OxyM, xM – Nasal drop (common cold)
* Vasoconstriction in nasal & eye → ↓ congestion → decongestants
* Naphazoline: Conjunctivitis.
* Oxymetazoline & Xylometazoline: Common cold.
* Rebound congestion – when drug get metabolism
* Repeated use → Atrophic Rhinitis (necrosis of tissues)

3) Midodrine, Methoxamine

* Used as tablet
* ~~Meth~~: Both vasoconstrict^n → ↑ BP.
* Rx: Chronic hypotension

α_2 agonist

- α_2A ↑↑ (CNS)
- α_2B ↑↑

* α_2A → CNS → Inhibit all centres of CNS
  - Vasomotor centre (x)
    - ↓ BP → Rx: HTN
    - Clonidine.
    - α-Methyl dopa. (Safest anti HTN in pregnancy) (DOC in PIH)

- Inhibit pain centre
  - Used as analgesics
  - Rx. of post operative pain
    * Dexmeditomidine

- Inhibit withdrawal centre
  - Used in Rx. of opioid withdrawal syndrome.
    * Lofexidine
    * Clonidine

- Inhibit muscle stretch reflex
  - Used as muscle relaxant
    * Tizanidine

- Reduces peristalsis
  - Used in Rx. of non-infective diarrhea (MOA not known)
    * Clonidine

- α_2B receptor agonist
  * Apraclonidine
  * Brimonidine
  - Both causes vasoconstrictn in ciliary body of eye
  - Used as eyedrop
  - ↓ blood supply to eye → reduced aqueous humour synthesis & filtration
  - Rx of Glaucoma.

* s/e of them
  1) ↓ Resp. centre → ↓ RR (resp. rate)
  2) ↓ VMC → ↓ HR (vagus motor centre) VMC
  3) ↓ glands → Dry mouth, dry eye.
  4) ↓ RAS (reticular activating centre) → Sedation & Drowsiness
     ↓
     MC s/e of them
  5) Clonidine → Constipation
  6) Clonidine → Rx. HTN → sudden withdrawal of clonidine therapy → rebound hypertensive crisis → k/a clonidine withdrawal syndrome

β-2 agonist

* β2 present everywhere
* ↑ cAMP
* Relax smooth muscle, but contracts cardiac muscle & skeletal muscle

⇒ Uterus
- Relaxed
- Used as tocolytic (in preterm labour) (< 37 wks)
  - Ritodrine
  - Isoxsuprine
- s/e → Pulmonary edema

⇒ Bronchioles
* Bronchodilation
* Rx. of COPD & Bronchial Asthma

β_2-agonist

Short acting β_2-agonist (SABA)
1) Salbutamol (inhal^n)
2) Terbutaline (subcutaneous)

Long acting β_2-agonist (LABA)
1) Salmetrol
2) Formetrol
3) Indacaterol (longest acting) ↓ (all inhalat^n)

* SABA is DOC for acute attack of COPD & acute attack of bronchial asthma
* LABA (long acting) given for maintanence Rx.
* SABA → Emergency
  LABA → OPD
* S/e :
  1) Hypokalemia (Salbutamol)
  2) Tachycardia (cardiac contract^n)
  3) ↑cAMP → skeletal muscle contraction → Tremors (MC)
  4) Vasodilation (cAMP - smooth muscle) → ↑ blood flow towards skeletal muscle → exercise capacity is improved → ↑ overall performance.

⇒ So Athelets, sportsmen are using for peformance enhancing (doping)

5) Hyperglycemia (β_2 on surface of liver → ↑ cAMP in liver → ↑ glycogenolysis & ↑ gluconeogenesis)

6) Tolerance (β_2↑ → long term stimulat^n → down regulation of β_2 ® → can't bronchodilate) k/a Tachyphylaxis

Indirectly acting sympathomimetics

* ↑ NAdr → acts on ® (so indirect stimulation of ®)

1) Enzyme inhibitor : (MAO inhibitors)
   * MAO I → ↑ NAdr in CNS (Depression)
   * Given mainly for Rx. of depression.

2) Reuptake inhibitor :
   * Reuptake of NAdr done by NAT (NorAdr transporter)
   * Reuptake inhibitor → ↑ NAdr
   * Antidepressants
     - TCA (Tricyclic antidepressant)
     - SNRI (Serotonin NorAdr reuptake inhibitor)

* Antiobesity (↑NAdr in CNS → inhibits appetite centres)
  - Sibutramine.
* Cocaine (local anesthetic)
  (↑NAdr in CNS, fast onset of action)
  So abused nowadays

mcq * Cocaine - Reuptake inhibitor of NorAdr.

mcq * Cocaine - Only local anesthetic which causes vasoconstriction (all others - vasodilatn)

mcq * Cocaine → snuffing → deposit on nasal septum → vasoconstrictn → gangrene → perforation in nasal septum.

3) Displacement of NAdr
* Drugs displaces NAdr in vesicle → NAdr comes out of vesicles to syn. cleft → ↑NAdr
  - Modafinil (↑NAdr → ↑CNS stimulatn → ↓ sleeping time → Rx. of hypersomnia)
* Hypersomnia in Narcolepsy, Obstructive sleep apnea.
  - Methylphenidate (↑CNS → ↑ attention span → Rx of ADHD (Attention Deficit Hyperkinetic Disorder)
  - Amphetamine (↑NAdr in CNS → ↓ appetite centre → Rx. of obesity.

* S/E →
1) Abusive liability (addiction)
   (MC used in Rave parties as Rave drugs - illegal drugs)
   - Amphetamine : Kick
   - MDMA : Ectasy (Methyl dihydroxy methyl amphetamine)

2) ↑NAdr → in CNS
   - Insomnia
   - Weight loss
   - Seizure

   in PNS
   - ↑HR
   - Arrythmia
   - HTN.

3) Food products (contains tyramine - acts like Amphetamine) (↑NAdr)
   ↓
   if use MAOI along with it
   ↓
   cannot metabolize NAdr
   → excessive NAdr →
   HTN crisis (Cheese Reaction)
   ↓
   Present in Cheese, Red wine, Fava beans.
   (Tyramine)

4) Insect toxin (↑ displacement of NAdr) → HTN crisis
   - Scorpion toxin
   - Black widow spider toxin

Mix action Sympathomimetics

- Direct action (+) (α, ↑↑)
  - ↓ Vasoconstriction
  - ↓ Rx. chronic ↓BP
  - ↓ Decongestant
  - ↓ ↑ tone of sphincter
  - ↓ So Rx. Stress incontence
    (seen in menopausal ♀ → loose bladder ⇢ when sneeze / laugh → ↑ stress → urine drops out)
  - ↓ For Rx. stress incontenence
    - Pseudo Ephidrine
    - Ephidrine
- Indirect action (↑ NAdr in CNS)
  - ↓ Rx. of obesity (suppress appetite centre)
    - Mephenteramine

SYMPATHOLYTICS

- α-Blocker
- β-blocker

α-Blocker

- Specific α-B < α_1 B, α_2 B
- Nonspecific α-B

* α_2 Blocker → Yohimbine
(Rx. of sexual dysfunction)

* α_1 blocker →
(1) • Prazosin
(2) • Terazosin
(3) • Alfuzosin
} Vasodilation

(Rx. of HTN, Peripheral vascular diseases)
↓
– Raynaud's disease

~~* Nonspecific α blocker~~

MOA
• Prazosin
↓
DOC for HTN crisis ↑ Toxin associated with
(Scorpion toxin, black widow spider)

* α_1 blocker –
(4) • Tamsulosin
(5) • Silodosin
(Both α_1 A ⊗ → prostate capsule → DOC for BPH)

* Non specific α - Blocker

- Reversible (electrostatic)
- Ergot derivatives
- Irreversible (covalent bond)

• Irreversible
– Phenoxybenzamine
(DOC of HTN crisis associated with pheochromocytoma (↑ adrenal medulla))

* Reversible
  - Phentolamine
    (DOC of HTN crisis associated with cheese reaction & clonidine withdrawal syndrome)

* Ergot derivatives
  (1) - Dihydroergotoxin
    (causes CNS vasodilation, ↑ blood supply to brain → remove free radicals from brain → Rx. of Alzheimer's disease which is mainly due to free radical injury)

  (2) Bromocryptine, Pergolide, Cabergoline
    ↓
    D_2 receptor ↑↑ in CNS
    ↓
    DOC for hyperprolactinemia, Rx. of Parkinson's disease.
    ↓
    Dopamine also k/a PRIH (prolactin release inhibitory hormone) (↓ prolactin)
    ↓
    Cabergoline - DOC for hyperprolactinemia
    Bromocryptin - " in pregnancy.

  (3) Ergotamine, Methysergide
    (acts on CNS - Serotonin : 5HT
    $5HT_{1B/1D}$ (R) → vasoconstriction in CNS → so used in Rx. of Migraine)

  4) Methylergometrine
    - strong uterine contraction
    - Rx. of PPH (post partum hemorrhage)

* s/e of Ergot derivatives:
  1) MC - Nausea & Vomiting
  2) Methysergide (migraine)
    → fibrosis as s/e
    Maximum fibrosis as s/e by Methysergide.
    → MC site of fibrosis is retroperitoneal fibrosis.
  3) Vasoconstriction → gangrene in organs supplied by end artery.
  4) LSD (Lysergic acid)
    (dopamine receptor - D_2 agonist
    → hallucination → abusive (hallucinating drug)
    (+ hallucination)

SYMPATHOLYTICS (continuation)

β-blocker

* Classification is
  1) Generation I : (Non specific)
    - Blocks β_1 & β_2.
      (β_2 (X) → vasoconstriction)
    - s/e is vasoconstriction

- Propranolol
- Timolol
- Sotalol
- Nadolol

2) Generation II (Specific)

* Blocks β_1 only
* β_1 → Cardiac cells, JG cells, ciliary body
* So k/a Cardioselective β-B
  - Atenolol
  - Betaxolol
  - Metoprolol
  - Esmolol

3) Generation III

* Have special vasodilator property.

(i) β⊗ + α⊗
- Labetalol
- Carvedilol

(ii) β⊗ + Ca^{2+}⊗
- Carvedilol
- Carteolol

(iii) β⊗ + Nitric oxide - NOTT
- Nebivolol.
- Esmolol.

■ Indications of β-blockers

1) HTN (Gen III → Labetalol, Esmolol)
↓
- fast acting so Rx. HTN crisis
- Labetalol - DOC of HTN crisis in pregnancy

(PIH → M-dopa → but slow onset of action)

BP = CO × PR (peripheral resistance)

- Gen II → β_1⊗ → ↓ BP → SO used for maintanence only.

2) Myocardial infarction & Angina

* β_1⊗ → ↓ HR → ↓ O_2 demand.
* Use gen II, sometimes generation III also.

3) Arrhythmia:

* Very very high HR
* β_1⊗ → ↓ HR
* Rx. Generation II.

4) CHF (Congestive Heart Failure)

- Decompensated HF → EF < 40% → Cardiogenic shock
- Compensated HF → EF > 40% but EF < 60%

* CO = SV × HR (SV-stroke volume)
  SV ∝ EF (ejection fraction)
* β⊗ → ↓ CO
* So C/I in cardiogenic shock (decompensated)
* But β⊗ can be used in compensated HF → because prevent remodelling (fibrosis of heart muscle)

* CHF → CO < (N) → ↓ renal blood flow → ~~Renin - Angiotensin~~ JG cells (β_1) → Renin → Ang I to Ang II by ACE → AT_1 (R) in adrenal cortex → ↑ Aldosterone (RAAS - Renin Angiotensin Aldosterone System) → (R) on heart muscles → fibrosis (↓ expansion) → end diastolic volume reduced (less amt of blood enter heart) → aggravates condition CO ↓↓ → again same cycle. → can lead to cardiogenic shock.

* So should prevent this → by giving ACEI, ARB, Aldosterone (R)⊗, β⊗ → reduces mortality of patient & ↑ survival of patient.

MIB

* β⊗ → Not used in acute cases - decompensated stages.

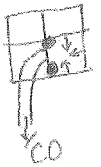
* But β⊗ indicated in compensated HF cases.

5) β⊗ are also used in mitral valve prolapse (MVP)

* Symptom → Severe tachycardia
* β⊗ → ↓ HR
* β⊗ are DOC in MVP (2nd gen)
* Best Rx. is surgery.

6) HOCM (Hypertrophic Obstructive Cardio myopathy)

(muscle on either side of vessel hypertrophy - ventricular → closes vessel → ↓ CO)



* β(x) reduces force of contraction (ionotropic) (↓)
* Given to improve CO.
* ↓ obstruction of aorta by hypertrophied muscle on base of aorta.

7) Lipid soluble β⊗ - Propranolol → cross BBB → acts on CNS → blocks effect of NAdr / β_1 in CNS → sedation, drowsiness (s/e) ↓ can treat anxiety with s/e ↓ β⊗ are DOC for performance anxiety.

8) Extrapyramidal s/e caused by antipsychotics → akathesia (absence of movement) → "restlessness" is symptom ↓ DOC is propranolol for this. ↓ Antipsychotics blocks dopamine

9) For opioid withdrawal syndrome → propranolol causes sedation & drowsiness → it is needed for Rx. of OWS.

(locus ceruleus) Withdrawal centre → ↑ NAdr → β_1 → symptoms (insomnia)

Propranolol → ⊗ → NO symptoms.

NOW - Withdrawal syndrome → insomnia, ↓ appetite, seizures.

10) Gen-1 β ⊗ → Vasoconstriction by
β_2 ⊗ → Prophylaxis of Migraine
→ DOC is Propranolol

11) Also DOC for prophylaxis for Oesophageal varices. (Propranolol)

12) Rx. of essential tremors (physiologic tremor in all old & few young which is not Parkinsonism)
- β_2 → Tremors
- Gen I β ⊗ : Propranolol is DOC ~~here~~ for essential tremors.

13) Pheochromocytoma → ↑NAdr excess → α_1 → HTN crisis → Hemorrhagic stroke → brain hemorrhage → also β_1 → ↑HR → Arrythmia
DOC : Phenoxybenzamine
Also can give β ⊗ to relieve β_1 → ↑HR → arrythmia

14) Rx. of thyrotoxicosis (excessive thyroid hormone - T_3) (↑T_3, ↑HR, Arrythmia (β_1), Tremors (β_2)
Propranolol blocks T_4 to T_3 conversion, blocks β_1 & β_2
DOC for thyrotoxicosis is Propyl thiouracil.

15) Glaucoma (ciliary body)
- Can give specific β_1 ®
- Also nonspecific (β_1 & β_2 ®)

(Nonspecific >> Specific)
- Specific β_1 (x) → Betaxolol
- Non specific β (x)
Timolol, Levobunolol

S/e of β-blockers

I) β_1 ⊗
- ↓HR
- ↓ Force of contraction
- ↓ conduction velocity
- ↑ dyslipidemia

II) β_2 ⊗ (Bronchoconstriction)
- precipitate bronchial asthma
- Also vasoconstriction → SD precipitate HTN crisis, peripheral vascular disease, erectile dysfunction, ↓ exercise performance as ↓ blood supply to skeletal muscle, hypoglycemia (inhibits glycogenolysis)

III) Lipid soluble β ⊗ → cross CNS
- Sedation & drowsiness
- Depression

C/I of β-blockers

* β_2 ⊗ → Not to vasospastic angina (also k/a Prinzmetal Angina) (less blood to heart due to vessel spasm)
* β_2 (x) → Not in bronchial asthma
* β_1 ⊗ → ↓HR < 50-60 b/min or S. bradycardia or stokes Adam syndrome or Sick sinus syndrome.

* β_1 ⊗ → ↓ EF < 40% / Acute decompensated HF / Severe HF (NYHA grade III & IV, NYHA - New York Heart Association) or Cardiac shock.
* When less conduction velocity or PR interval > 0.2 sec or partial heart block.
* Hypotensive shock or BP < 90/60

Toxicity of β-blocker

* DOC for β⊗ toxicity is Glucagon.

Pharmacokinetics of β-blockers

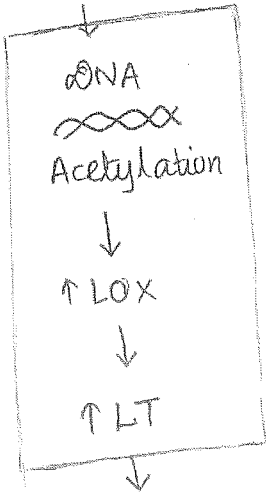
* Lipid soluble are (liver metabolism)
  - Propranolol
  - Metoprolol
  - Labetalol
* Lipid insoluble β⊗ are (kidney elimination)
  - Atenolol
  - Nadolol
  - Sotalol

ANS

* t½ of β⊗
  * Longest acting
    Nadolol >> Sotalol
  * Shortest acting
    Esmolol
* Esmolol is metabolized by RBC using Esterase enzyme (8-10 min) t½

Respiratory System

* Pathophysiology ⇒ Allergen (Type 1 hypersensitivity →
  ↑ IgE → Mast cells
  ↓
  IgE
  ↓



(LT: Leuko trienes)

  ↓
  LT release from the mast cells.
  ↓
  It causes bronchioles inflammation
  ↓
  Bronchospasm
  ↓
  Bronchial asthma.

* Medicines which ~~block~~ relieve bronchospasm → Bronchodilators
* Block LT, LOX, Acetylation, IgE.

Bronchial Asthma

- Bronchodilators → Symptomatic relief.
- Anti-inflammatory drugs. (CS, IgE, LOX, Mast, LK) → Rx. cause of conditions

Bronchodilators:

1) β2 agonists:

- SABA: DOC → acute attack
  Salbutamol, Terbutaline
- LABA:
  - Indacaterol (longest t½)
  - Salmetrol (2nd long t½)
  - Formetrol (fastest acting)
    (Given for acute episode & maintanence both)

* s/e:

- Tremors
- Hypokalemia
- Tachycardia
- Vasodilation
- Hyperglycemia
- Tolerance.

* Directly acting drugs.

2) Parasympatholytics:
↳ M_3 blocker

- Ipratropium bromide } inhalational
- Tiotropium bromide }

3) Catecholamines

- Adrenaline } Rx. status asthmaticus.
- Isoprenaline }

4) $MgSO_4$.

- Given i.v
- Ca^{2+} → enter → bronchial muscle → contraction
- Body cannot differentiate blw Ca^{2+} & Mg^{2+}
- Here $MgSO_4$ → Mg^{2+} → enter bronchial muscle → blocks Ca^{2+} entry → prevents contraction → bronchodilation.

5) Methyl xanthines:

- Theophylline
- Derived from chemical compounds in tea & coffee
- MOA -
  (i) Phosphodiesterase enzyme inhibitor is theophylline
  cAMP & cGMP is metabolised by phosphodiesterase → when it ⊗ → ↑ cAMP & cGMP → relaxation of bronchial muscle
- s/e → ≈ β2 agonist
  (Tremors, tachycardia, Hyperglycemia, vasodilat°)

- MOA:
  (ii) Theophylline is blocker of adenosine receptor → B.dilatn
  (iii) Theophylline → ↑ histone deacetylase enzyme in nucleus of mast cells.
  Remove acetyl group → so no acetylation → ↓ expression of gene → no LOX → B.dilatn.

■ Pharmacokinetics of Theophylline
  * Given oral
  * Aminophylline → i.v → status asthmaticus (form of theophylline)
  * Plasma → lipid soluble → cross BBB → acts on CNS → stimulate CNS.
  * s/e: Insomnia, Seizures, reduced appetite
  * Plasma → it has narrow therapeutic index (narrow concentration range it is beneficial to the patient)
  5-20 µg/L in plasma.
  ↓
  if level > 20 µg/L ⇒ Toxic
  < 5 µg/L ⇒ No action
  ↓
  Needs strict monitoring k/a therapeutic drug monitoring (monitoring of drug in plasma)
  * Metabolized by liver.
  (by CYP 1A2 enzyme of liver)
  ↳ Zero order kinetics.

■ Indications of Theophylline
  1) Bronchial Asthma
  2) COPD
  3) Apnea of newborn (stimulate respir. centre)

■ s/e of Theophylline:
  * Nausea & Vomiting
  * (↑cAMP ≈ β2↑) s/e
  * CNS stimulation (insomnia)

Anti-inflammatory

1) Corticosteroids:
  * MOA: Acts on nucleus of mast cell → ↑ histone deacetylase → removes acetyl group → ↓ LOX expression (Antiinflammatory effect).
  * DOC for maintainence of bronchial asthma.
  * Route - Inhalational / oral / i.v
  * i.v → Hydrocortisone (status asthmaticus)
  * Oral → Prednisolone (severe bronchial asthma)
  * Inhalation → MC & Best
    - Budesonide
    - Ciclesonide
    - Fluticasone (most potent)
    - Beclomethasone
  * s/e →
  Inhaled:

* Inhaled corticosteroid s/e
  (1) Oral candidiasis (steroids deposit in buccal cavity → immunity of buccal cavity ↓) also k/a Oral Thrush.
  (Mouth rinsing is advised after taking drug, or take medicine with the help of spacer
  (2) Change of voice (Dysphonia) (thickness of vocal cord ↑)
  (3) Systemic s/e :
    i) CNS → ↑ ICT, psychosis, Epilepsy (intracran. tension)
    ii) Eyes → Cataract
    iii) CVS → Hypertension
    iv) Blood → ↓WBC, immuno-compromised
    v) GIT → ↑ Acid (peptic ulcer disease)
    vi) Musculoskeletal – Osteoporosis, avascular necrosis of femur head, atrophy of muscle & skin.
    vii) Endocrine – Suppress HPA axis (Hypot. pitu. adrenal)
    viii) Metabolic pathway –
      • Central obesity
      • Hyperglycemia

2) IgE inhibitor :
  • Omalizumab
  ↓
  for maintanence Rx. of bronchial asthma (steroid resistant B. Asth.)
  ↓
  Subcutaneous route
  ↓
  s/e – Hypersensitivity reaction. (-zu-, -xi-)

3) Anti-inflammatory
  * LOX ⊗ → Zileuton
  * s/e : Liver toxicity (so outdated)

4) Leukotriene ® ⊗
  • Montelukast
  • Zafirlukast
  * s/e – Rarely, Churg straus syndrome

5) Mast cell stabilizers :
  * MOA → K^+ channel opener → acts on mast alls → open K^+ channel → K^+ moves out (efflux) → cell become hyperpolarised → inhibits LT release → no inflammation.
  • Nedocromil sodium
  • Sodium Cromoglycate
  • Ketotifen
  * All are used for Rx. of allergic conjunctivitis (eye drops)

COPD

* Empysema & chronic Bronchitis
* Bronchodilaters are useful for COPD Rx. (5-Bronchodilator)
* SABA → DOC - Acute attack
  M_3 ⊗ → DOC for maintanence Rx. of COPD
* No need for ~~anti-inflammatory~~ anti-inflammatory.

COUGH

Dry → (Antitussives) → ↓
* DOC - Opioids
* MOA - Cough centre ↓↓ (CNS)
  - Codiene
  - Noscapine
  - Dextromethorphan

Wet (with sputum) → ↓ (Expectorant)

Expectorant

- Ambroxol
- Bromhexine
- KI, NaI,
- Lugol's iodine
- Guaphenisin (natural)

Mucolytics

- Acetyl cysteine

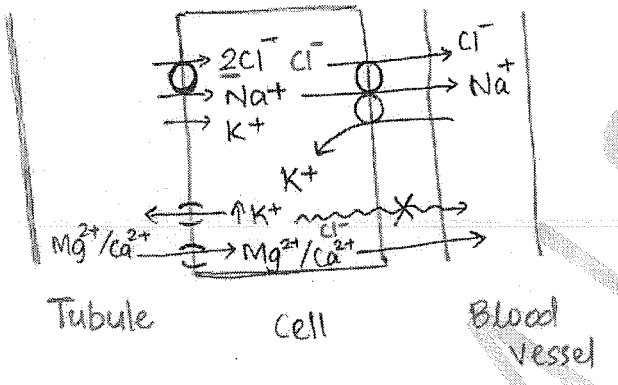
* Breaks down mucus plug during bronchial asthma.
* ROA: i.v
* DOC in Paracetamol poisoning

KIDNEY

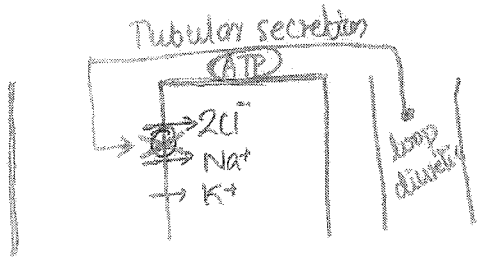
* Drugs acting on tubules → Diuretics
* Ions are absorbed in tubules
* Nephrons → Bowman's capsule + Tubule
* 65% Na^+ reabsorbed in PCT (via multiple channels)
* 20% Na^+ → Ascending LH (via $Na^+ - K^+ - 2Cl^-$)
* 10% Na^+ → Early DCT (via $Na^+ - Cl^-$ channel)
* 2-3% Na^+ → Late DCT & cortical CT (via Na^+ reabsorb, K^+ & H^+ secreted)
* 2-3% Na^+ lost in urine.

1) Loop diuretics:

* Site ~~of~~ of action → Thick part of Ascending limb of LH.
* MOA : $Na^+ K^+/2Cl^-$ pump ⊗
* Efficacy → 20% Na^+ & H_2O loss (20%)
* Most powerful & most efficient diuretics.
* Body will activate some compensatory mechanism to minimize the Na^+ loss. But it cannot overcome the diuretic effect.



* $Na^+K^+/2Cl^-$ → from tubule to cell → Na^+ with 1 Cl^- or Na^+ with K^+ → Na^+ to blood plasma → K^+ ↑ in cell → cant go to blood → go to tubule with antiport of Mg^{2+}/Ca^{2+}
* With the help of tubular secretion through ATP pump, inhibits $Na^+K^+/2Cl^-$ symport in the tubule



* From blood vessel → loop diuretics acts via tubular secretion → blocks the $Na^+K^+/2Cl^-$ symport → ~~prevents loss of~~ causes Na^+ loss.

* s/e of loop diuretics

1) Electrolyte imbalance
   - (Na^+, K^+, Cl^- ↓) (Hyponatremia, hypokalemia, hypochloremia)
   - Also ↓Mg^{2+}, ↓Ca^{2+} (hypomagnesimia, hypocalcemia)
   - There is ~~loss of~~ reflex phenomenon → it tries to re'absorbs Na^+ from late DCT & CT → leads to loss of K^+ & H^+
   - Reflex loss of K^+ & H^+ (hypokalemia, alkalosis)

2) Sensory neurotoxicity
   - Sensory nerves are highly dependent on Na^+
   - Parasthesia, taste change, ototoxicity

3) Metabolic s/e:
   - Hyperuricemia (↑uric acid)
   - Hyperglycemia
   - Hyperlipidemia

4) Calcium stone

■ Indication:

1) CHF (Congestive Heart Failure)

- (↓ blood pump → muscle ineffective → ↑↑ congestion → heart muscle stretches → blood vessels in b/w muscles get constricted → ↓ bloodsupply to heart → ionotropic effect ↓ → ↑ congestion)
- Diuretics → 20% Na^+ & H_2O loss → ~~blood supply~~ ~~ionotropic~~ ~~blood supp~~ blood volume ↓ → ↓ congestion → less stretch → ↑ blood supply to heart.
- CHF (stable) → ↓ renal blood flow → ↑ RAAS → ↑ Na^+ & H_2O reabsorption → ↑ congestion.
- In CHF → diuretics is used to → ↓ congestion.

  * Furosemide.
- CHF → blood in LA to PV → lungs → pulmonary edema.
- Furosemide is a strong venodilator (dilates the vein) → more blood in periphery → less blood to heart → ↓ congestion
- Artery : Resistance vessel
  Veins : Capacitance vessel
- DOC for pulmonary edema by CHF → Furosemide.

2) HTN crisis

* Furosemide → Na^+ & H_2O loss → ↓ BP

3) Hypercalcemia

* ✱ Ca^{2+} absorption ⊗ directly

✱) Edema. (Non specific)

- Torsemide.

■ C/I of loop diuretics

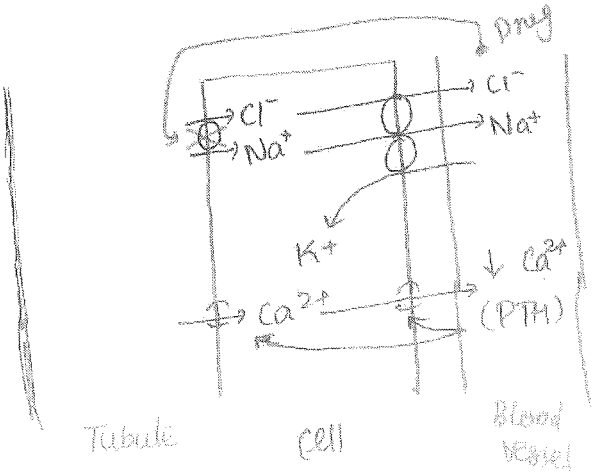
1) If patient is a known case of ~~sulpharamide~~ drug allergy (sulfonamide)

■ Loop diuretics eg:

- Bumetanide
- Ethacrynic acid.

2) Thiazide diuretics

* Site of action → Early DCT
* MOA → Na^+Cl^- ⊗
* Efficacy → 10% Na^+ & H_2O loss (intermediate efficacy)
* Compensatory mechanism can overcome the effect of it



* Whenever ↓ Ca^{2+} in blood → PTH → via special Ca^{2+} channels → Ca^{2+} reabsorption.
* Tubular secretion of drug with the help of ATP pump (from the luminal side) → block Na^+Cl^-
* S/e - Same as loop diuretic
  - But no ↓ Ca^{2+} ∴ no Ca^{2+} stone.
* Indications
  1) Mild-Moderate HTN
  2) Diabetes incipidus (excessive loss of water from the body)
     ↓
     Due to ↓ ADH (by post. pituitary)
     → loss of H_2O → called as central diabetes incipidus.
     ↓
     Also ADH acts on V_2 receptor
     → V_2 receptor is down regulated
     → Nephrogenic D.I.
     - Hydrochlorthiazide (HCTZ)
     ↓
     Causes 10% Na^+ & H_2O loss
     → ↑ compensatory mechanism
     → ↑ ADH secretion & up regulates V_2 receptor.
     ↓
     So given for both central & Nephrogenic D.I
     ↓
     - DOC for nephrogenic D.I
       - Thiazide diuretics
     - DOC for central D.I
       - Desmopressin
  3) For Rx. hypocalcemia
     - In presence of HCTZ, PTH action ↑↑ → ↑ Ca^{2+} retention.
* C/I of thiazide.
  - If patient is a known case of sulphonamide drug allergy.

Loop diuretics

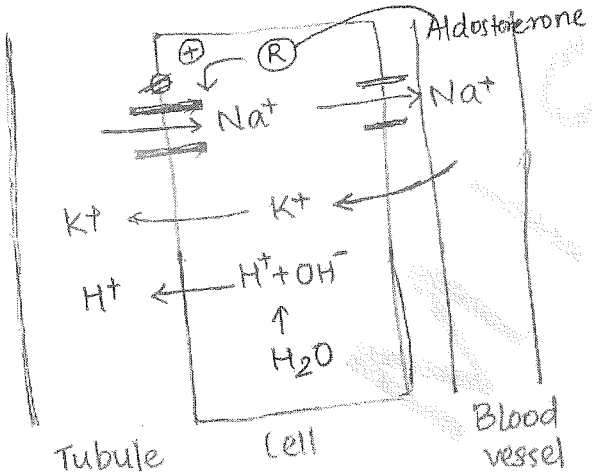
* SOA: Ascending loop of Henle (thick part)
* MOA: $Na^+ K^+ 2Cl^-$ ⊗
* 20% efficacy
* Compensatory mechanism cannot overcome
* Use
  1) CHF
  2) Edema
  } ↓ Na^+ & ↓ H_2O
  3) HTN crisis
  4) ↑ Ca^{2+}
* S/e
  - Loss of all ions

Thiazides

* Early DCT
* Na^+Cl^- ⊗
* 10%
* Can overcome
* Use
  1) Diabetes incipidus (↑ H_2O retension)
  2) Mild-mod HTN (maintanence Rx)
  3) ↓ Ca^{2+}
* S/e
  - All ion loss, except Ca^{2+}

3) Pottasium sparing diuretics:

* SOA : Late DCT & cortical CT
* MOA (i) Na^+ channel Ⓧ
  - Amiloride
  - Triamterene
  (ii) Aldosterone receptor Ⓧ
  - Spironolactone
  - Epelerenone
* 2-3% loss of Na^+
* Low efficiency diuretics
* Compensatory mechanism can overcome its effect.



→ (Ⓡ in cytoplasm)

* Aldosterone released → when ↓ H_2O → ↑ Na^+ reabsorption → more H_2O reabsorption.
* ADH also acts → when ↓ H_2O → ADH Ⓡ +nt on membrane surface → V_2 → ↑ cAMP → AP-2 (aquaporin) → opens → H_2O reabsorped.

* s/e
  1) ↓ Na^+ (2-3%)
  2) ↑ K^+ in plasma (hyperkalemia)
  3) Spirolonolactone → blocks aldosterone Ⓡ & testosterone Ⓡ → erectile dysfunction, ↓ libido, ↑ estrogen level in ♂ - gynaecomasia.
  ~~[~~Epelerenone will not ~~use~~ Ⓧ testosterone Ⓡ → so can be given in male~~]~~
  4) Triamterene → deficiency of bonemarrow, folic ~~marrow~~ acid deficiency. (outdated) ↓ Now used is Amiloride.

* Indication:
  1) CHF (prevents re-modelling by Aldosterone Ⓡ blockers)
  2) DOC for Ascites (Aldosterone Ⓡ Ⓧ)

(Liver failure → ↓ plasma protein → ↓ plasma osmolarity → Ascites → ↓ plasma volume → ↓ RBF → ↑ RAAS → ↑ Aldosterone → Ⓡ* → ↑ H_2O & Na → plasma volume Ⓝ ↑

  3) Hirsuitsm (excessive facial hair growth in females) (due to T androgen) Spirolonolactone
  4) Used in Rx. of Conn's syndrome (↑ Aldosterone secretion) Ald. Ⓡ Ⓧ

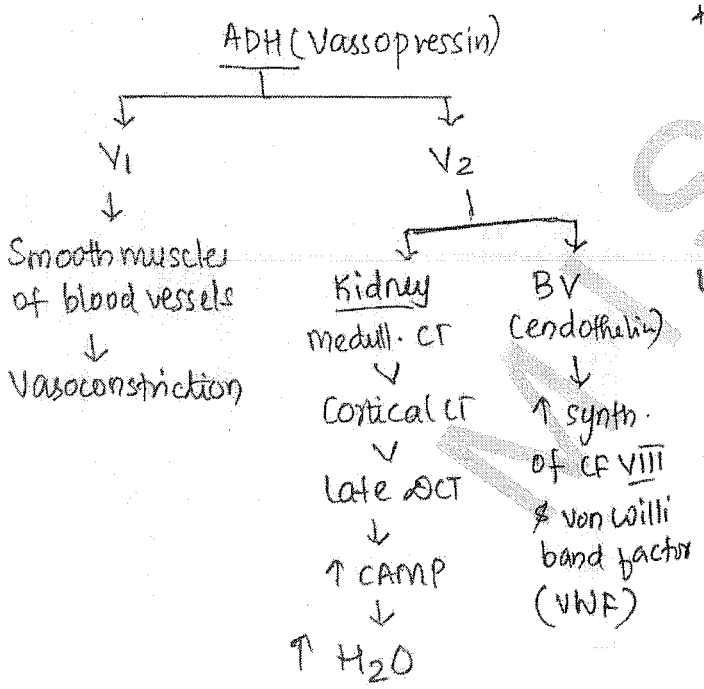
5) Used along with loop diuretics to prevent hypokalemia.

6) Amiloride is DOC for lithium induced diabetes incipidus & Lithium induced polyuria.

C/I

1) CRF (Chronic Renal Failure)
2) ACE I / ARBs cannot use along with it (K↑ is s/e)

4) Drugs acts on ADH pathway.

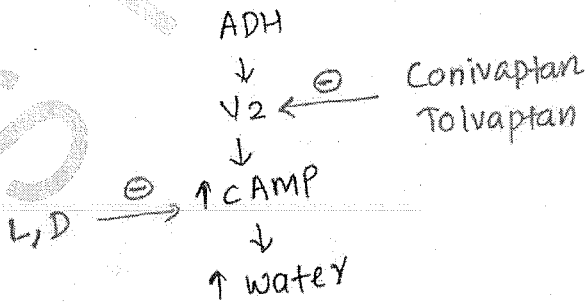


* V_1 receptor agonist:
  - Terlipressin
* V_2 receptor agonist
  - Desmopressin

* Terlipressin → Rx. of acute hypotension, bleeding oesophageal varices

* Desmopressin → DOC for central diabetic incipidus.
  ↓
  Also as DOC for nocturnal aneuresis
  ↓
  DOC for clotting factor VIII deficiency hemophilia
  ↓
  DOC in VWF deficiency disease. (RxOC - Blood transfusion)

* Desmopressin → Oral / N.S.
* Terlipressin → i.v route.



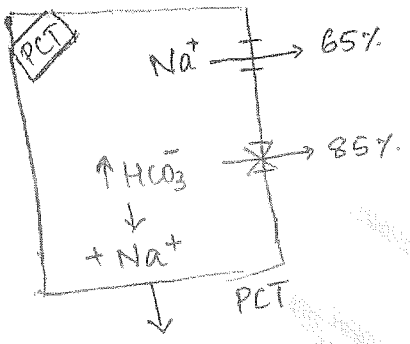
* V_2 ⊗ inhibitor:
  - Conivaptan
  - Tolvaptan.

* Inhibitor of cAMP
  - Lithium
  - Demeclocycline

* ADH inhibitors are used for Rx. of SIADH (Syndrome of inappropriate ADH) (4 drugs

5) Carbonic Anhydrase inhibitors

* SOA : PCT
* MOA : ⊗ CA enzyme (Non competitive)
* Inhibits HCO_3^- absorption (85%)
* Along with HCO_3^-, Na^+ ion is also lost.
* Efficacy - low efficiency diuretics
* Compensatory mechanisms can easily overcome the effect of them.



* s/e :
  1) Metabolic acidosis ($\downarrow$ 85% HCO_3^- ions)
  2) $\downarrow Na^+$ (mild)
  3) Alkaline urine → Ca^{2+} precipitates in alkaline urine ($CaCO_3$) → Ca^{2+} stone formation.
  4) Loss of K^+ & H^+ (alkalosis) But acidosis predominates over alkalosis.

* Indications
  1) Glaucoma (CA enzyme on surface of ciliary body → takes HCO_3^- & forms aqueous humour → hence ↓ aqueous humour synthesis)
     - Brinzolamide } eyedrop
     - Dorzolamide }
     - Acetazolamide (oral/i.v)
  2) Mountain sickness (Acute mountain sickness)
     * Higher altitude → hypoxia → hyperventilate → CO_2 washout → resp. alkalosis → symptoms of mountain sickness (N, V, insomnia)
     * Azetazolamide → induces metabolic acidosis → neutralizes alkalosis → DOC for acute mountain sickness.
  3) Epilepsy:
     * Due to ↑ ICT (↑ CSF) → HCO_3^-
     * CA takes HCO_3^- from plasma & to form CSF (HCO_3^- imp component in CSF)
     * CA ⊗ → ↓ CSF synthesis → ↓ ICT

* C/I
  1) CRF (M. acidosis already ↑nt)
  2) COPD (↑ CO_2) (R. acidosis)
  3) Liver failure (precipitate encephalopathy)
  4) Known case of Sulphonamide HSN ⊕ (HSN + → Hypersensitivity reaction)

6) <u>Osmotic diuretics</u>

- Mannitol (i.v)
- Glycerol (oral)

* Both are chemically neutral
* No entry to any tissue
* Medicine → plasma → filtered to kidney through bowmann's capsule → in PCT produces osmotic effect → binds to H_2O → this H_2O cant reabsorp → so loss of H_2O → ↑ urine output.
* Maximum in PCT of kidney.
* <u>Indications</u>

1) Cerebral edema
   (H2O from edema of brain tissue absorbed to cerebral artery)
2) DOC for acute angle closure glaucoma.
   Mannitol (iv)
   (H_2O not available for aqueous humour)
   - Most powerful medicine to reduce aqueous humour production
3) Rx. of Oliguria.

<u>Miscallenous group</u>

Natriuretic peptides:

* ↑ Na & H_2O loss
* ANP analogue – <u>Carperitide</u>
* BNP analogue – <u>Nesiritide</u>
  (natural peptide) (drugs)

<u>General Pharmacology</u>

PK (body on drug)

✓ ROA
↓
✓ Absorption (AUC)
↓
✓ Distribution (Vd)
↓
Targets
↓
Action (log DRC)

PD (Drug on body) – Targets, Action

↓
✓ Metabolism
↓
✓ Elimination (NE, RE, C_L, $t_{1/2}$)

<u>ROA</u>

* Route of Administration
* (MCQ) MC ROA is Oral
* (MCQ) Compliance is max. with oral (comfortable)
* Best route is i.v
* Monitoring is easiest with i.v

* Others → intramusular (i.m), subcutaneous, i.d; sub.L.

* i.m → Rich vasculanity so high rate of absorption. (fast)
  ↓
  - So used in acute emergency
  - If anticoagulant therapy (clotting mechanism inhibited) should avoid i.m → risk of bleeding (highly vasular)

* Subcutaneous (s.c)
  - Rate of absorption is slow due to less vasulanity
  - So can't be used during acute emergency

* Intradermal
  - Used during BCG vaccination, to check drug sensitivity, also in Montex test, in allergen desensitivity.

* Sublingual:
  - Nitroglycerine in acute Angina
  - Fastest onset of action. (less distance to superior venacava)
  - We can stop the action immediately by spitting out whenever we want
  * So can prevent s/e
  - So best in acute angina.
  - First pass metabolism by liver is prevented.

* Rectal:
  - Diazepam, Paracetamol
    ↓
    Febrile seizures.
  - First pass metabolism is avoided & in child (not willing to take orally)
  - But uncomfortable.

* Inhalational route:
  - Medicine is the site of pathology → Local route
  - Otherwise → Systemic route
  - eg: General Anesthesia.
  - Rate of absorption is fast due to ↑ surface area. MCQ

* Local route:
  1) Topical → Directly applied
  - Ointment > Gel > Lotion
  - Ointment has more oil content & less H_2O content → so more lipid soluble → max. action
  - Lotion has more water content and less oil → less penetration → less action.
  - Gel → in b/w action & content

2) Deep tissue injection:
- Intravitreal
- Intra articular

3) Intra arterial route
- Eg: Osteosarcoma → apply tornique (compress vein) → give anticancer drugs via intra arterial → it will stay at the site of action.

* Skin patch
- Lipid soluble drugs.
- But absorption is slow
- So used for maintainence not in acute emergency.
- Rate of absorption ∝ 1/thickness of stratum corneum.
- Thickness of stratum corneum (skin) is minimum in Post. auricular > facial skin > Scrotum > skin of other body regions > skin of palms and soles. (maximum thickness)

Absorption of Drug

* Amount of drug which reaches at the level of plasma in its unchanged form.
* Also k/a Bioavailability
* Calculated as % (percentage)

eg: [A] → 100mg i.v → 100%
→ 100mg → oral - 60mg → 60%

* Factors

(1) Surface area of absorbing surface.
↑ SA → ↑ Rate of Absorption

(2) Route of administration
Drug → i.v → 100%.
→ any other route → <100%

(3) Oral route
- Lipid soluble drugs can easily cross intestine & reach plasma
- ↑ lipid solubility → ↑ absorption

(4) Vascularity:
- ↑ vascularity → ↑ absorption
- Max. vascularity in im > sc.

(5) First pass metabolism
Metabolism of drug which takes place before reaching the systemic circulation.
- Oral → drug → portal vein → liver → hepatic vein → IVC → systemic circulation.
- ↑ FPM → ↓ Absorption / ↓ Bioavailability
- Eg: of drugs with high FPM

- Nitroglycerine → has high FPM
  So in acute angina given by sublingual except oral route to bypass FPM.
- Hydrocortisone → Rx of hypersensitivity → always given i.v.
- Testosterone → always given by i.m to bypass FPM
- Lidocaine → i.v
- salbutamol → Inhalation
- Propranolol, Opiods } But still given orally. Here given TDS

(6) Food in GIT

Food & drug has to absorp so when drug is consumed after food then it will ↓ absorption of drug.

- But some exceptions → ↑ absorption if given after food.
  i) Albendazole (Antihelminth)
  ii) Lumefantrine (antimalarial)
  iii) Greisofulvin (Antifungal)
  iv) Protease inhibitor (Antiviral) (HIV)
  v) Erlotinib (Anticancer)

(Usually ~~all~~ does most drugs are given after food → ie, to ↓ acidity → ~~not~~ no role in influencing absorption rate)

7) pH of surrounding medium

- Like is absorbed in like media
  eg: Acidic drug abs. in acidic media.
- So acidic drugs are absorbed from upper part of GIT
- Basic drugs are absorbed in lower part of GIT.

Calculation of drug absorption

1) Oral route → drug absorbed from GIT at different pH →
   Drug absorbed at a particular pH is calculated by Henderson Hasselbach equation

$$pH = pK_a + \log \frac{[\text{Ionic}] \text{ or polar}}{[\text{Nonionic}] \text{ or non polar}}$$

- pK_a → Dissociation constant
  It is the pH at which 50% drug is ionic & 50% drug is non-ionic.

$$pH = pK_a + \log \frac{50\%}{50\%}$$

$$pH = pK_a + \log 1 \quad (\log 1 = 0)$$

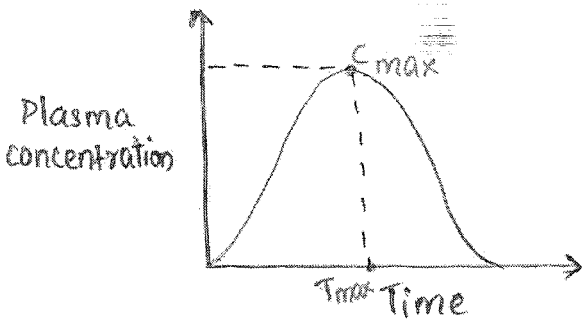
$$pH = pK_a$$

$\log 10 = 1$
$\log 100 = 2$

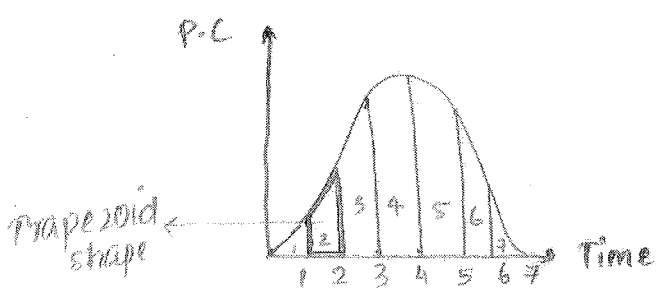
- If pK_a of a drug is 7 it means at pH = 7, 50% of drug is absorbed & 50% of drug can't be absorbed.
- Single change in pH → 10 times ↑ in $\log \frac{[\text{Ionic}]}{[\text{Nonionic}]}$ (pH 5 → 6 : $\log \frac{10}{1}$ → $\log 10$)

ionic drug → cannot absorbed
nonionic drug → can get absorbed.

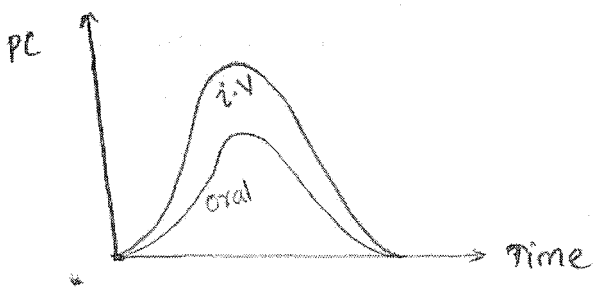
2) Drug absorbtion when given by another route
↓
Best parameter to calculate drug absorption / bioavailability is
Area under the curve.



- As medicine is taken → drug is absorbed from GIT → so plasma concentration ↑ with time → but liver enzymes ~~after~~ also activated and it will cause fall in drug concentration (as get metabolized)
- Cmax → Maximum concentration achieved in plasma after giving a particular dose.
- Tmax → Time taken to reach C_{max}



∴ Amount of drug absorbed = $\int$ Area of trapezoid 1–7
(Sum of all)



If area of i.v = 80, oral = 40
i.v has 100 % bioavailabity

∴ 100 % → 80 —— ①
? → 40 —— ②

$$x = \frac{40}{80} \times 100$$
$$= 50\ \%$$

$$\text{Bioavailability } x\ (\%) = \frac{\text{Area under curve } (x)}{\text{AUC (i.v)}} \times 100$$

Distribution

* It is defined as volume of distribution
* Volume of distribution is a hypothetical fluid in which drug is dissolved in patient body

eg: Drug A → given i.v/any route
100 mg

But if it is 100 % lipid insoluble it can't get in to organs so remain in plasma only.

V_d = 5L, Concentration = 1 mg/L
(5/5)

$V_d = \frac{\text{Dose administration}}{\text{Plasma concentration}}$

(V_d : Volume of distribution)

If dose = 100 mg, PC = 0.1 mg/L

$V_d = \frac{100}{0.1} = 1000\,L$

eg: 100 mg (100% lipid soluble)

↓

5 L plasma + 10 L (organs) = 15 L

Obese patient has extra compartment – adipose

5L + 10L + 5L = 20L.

- So in lean patient drug distributed in 15 L
- But in obese → distributed in 20 L → so need high dose.

* Factors affecting Vd :

1) ↓↓ Lean : Obese ↑↑
2) ↓↓ Normal ♀ : Pregnant ♀ ↑↑
3) ~~Add~~ ↓ Child : ↑ Adult
4) ↓ Normal : Edema ↑↑
5) ↑↑ Normal : Dehydration ↓
6) ↓ Young : Old ↑↑.

(more muscle, less adipose) (less muscle, more adipose)

Vd of Adipose ↑↑ > Muscle.

7) Plasma protein binding (after binding size of drug ↑, remains in plasma only) → Vd ↓

↑↑ Binding → Vd ↓↓ (Large size)

Plasma protein binding

* Albumin & α_1 acid glycoprotein can bind to drug.
* Albumin binds to acidic drug
* α_1 AGP binds to ~~albu~~ basic drug
* Acid drugs are (most of drugs are acidic)

MCQ
- Barbiturates
- Phenytoin
- Heparin
- Warfarin
- Penicillin-G
- Probenicid
- Methotrexate
- NSAIDs

* Basic drugs → Alkaloids (Plants / trees)

MCQ
- Pilocarpine
- Physostigmine
- Atropine
- Hyosine
- Digoxin (heart failure)
- Morphine (painkiller)
- Quinine (malaria)
- β blockers
- Amphetamine

* Clinical importance :

1) ↑↑ binding → ↓↓ Vd
2) ↑↑ binding → $t_{1/2}$ ↑↑

(bound form cannot be metabolized so remain in plasma)

3) Bound portion of drug is not available for action.

4) Bound form is not available for hemodialysis (cannot filtrated from the filter of hemodialysis as large size)

5) Displacement reaction: If two drugs are given which has same nature to the molecule → the one drug with ↑ affinity for protein can displace the drug with less affinity.

eg: NSAIDS & methotrexate → Albumin

* V_d = Dose Administration / Plasma concentration (PC)

∴ Dose administration = $V_d \times PC$

MCQ

$$\text{Dose} = V_d \times PC$$

Target:

* Drug binds to target in the required site
* If it production action at any other sites → ↓, s/e.
* MC target is Receptor
* Then enzymes, transporters & ionic channels.

Receptor

* Based on location
  - Membrane
  - Cytoplasm
  - Nucleus.

* Nucleus → Levothyroxine (T_4)
  (1) binds
  (2) Vit D
  (3) Estrogen (but main receptor in cytoplasm)

* Cytoplasm ⇒
  1) All steroids
  2) Estrogen

* Cell membrane: Two types of 2° messenger
  - GPCR (G-protein coupled Receptor) → 2° messengers are IP_3, cAMP, DAG → All others.
  - Tyrosine kinase → Needs 2° messenger JAK/STAT → - Insulin (PIG) - GH - Prolactin.

* IP_3 → Inositol triphosphate.
  DAG → Diacyl glycerol.
  cAMP → cyclic AMP.

Enzymes:

* All medicines are enzyme inhibitors.
* Inhibits enzyme by

Reversible
(Electrostatic bond)
(weak bond)

Irreversible
(covalent bond)
(strong bond)

- AChE ⊗ { - Organophosphates, - Carbamates, - Exemestane (Aromatase ↓ inhibitor), ± Aspirin.

Competitive
- Vmax → (N)
  Km → ↑↑
- Majority of drugs are

Phosphodiesterase enzyme ⊗ { 2) Theophylline, 3) Sildenafil

4) Digoxin. (Na^+K^+ ATPase ⊗)

GST
DD. PP

5) PPI (H^+K^+ ATPase ⊗)

6) Propylthiouracil (Peroxidase ⊗)

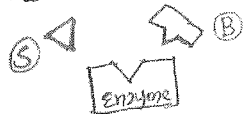
7) Disulfiram (Aldehyde dehydrogenase ⊗)

Noncompetitive
- Vmax → ↓↓
- Km → (N)

↓

1) Galantamine AchE ⊗

Competitive
(structure of blocker resembles substrate)



↓

According to the concentration of S & B, it will bind to enzyme.

↓

Blocker will bind to the substrate binding site.

↓

We can overcome this block by ↑ conc. of substrate
(Surmountable)

Noncompetitive
(no resemblance)

↓

Blocker will bind to a site other than substrate bindingsite k/a Allosteric site

↓

When blocker binds to allosteric site, it will alter the subs. binding site structure on enzyme.

↓

So substrate can't bind to enzyme

↓

We cannot over this by ↑ substrate conc.
(Insurmountable)

Transporters

inhibited by

* VAT ⊗ → Vesamicol
* VMAT ⊗ → Resenpine.
* NAT ⊗ → TCA
* SERT ⊗ → SSRI
  (Serotonine reuptake transporter)
* GAT ⊗ → Tiagabine
  (Gabba transporter)

NAT : Nor Adrenaline transporter

Ionic channels

- Na^+
- Ca^{2+}
- K^+

* Na^+ → depolarising ~~(i.e. inhibiting)~~

Na^+ ⊗ 1) Local anesthetics
2) Antiarrythmic
3) Antiepileptics

* Ca^{2+} Blockers

(i) T type Ca^{2+} channels
In CNS, nerve
- Antiarrythmic
- Antiepileptic

(ii) L type Ca^{2+} channels
In CVS
- CCB (Verapamil, Amlodipine)

(iii) S type Ca^{2+} channel (acts on brain)
No ⊗

* K^+ channels → Hyperpolarising

K^+ open 1) Minoxidil
2) Diazoxide
3) Mast cell stabilisers.

- Blocks K^+ channel
1) Sulfonyl ureas (Rx. of DM)
(DM: Diabetes Mellitus)

Drug Action

* It is described by 2 theories
1) Clark's receptor theory
2) Receptor Equilibrium theory

* Clark's receptor theory:
When drug is given to a receptor → they binds and forms D-R complex → then produce action
eg: Paracetamol → COX enzyme
receptor → ⊗ COX

D + R → DR complex → Action

Affinity
↓
Power of a drug to bind C receptor
- High → ↑↑ Action
- low → ↓↓ Action

Intrinsic activity
↓
Total functional change produced by a drug at the receptor site
↓
-1 to +1
(-1 0 +1)
↓
- (+1) → Full agonist
eg: Benzodiazepine (BZD)
↓
$GABA_A$ ↑↑
↓
Sedation & Drowsiness.

- ~~0 to +1 → Partial agonist~~
- ~~0 → Agonist Antagonist~~
eg: ~~Flumazenil : $GABA_A$~~

Intrinsic activity

- 0 to ± → Partial agonist
- 0 → Antagonist.
  eg: Plum
- -1 → Inverse agonist
  DMCM (β-carboline)
  ↓
  ↑ $GABA_A$
  ↓
  CNS stimulation

(Same $GABA_A$ is ↑ by B2D then causes opposite action sedation & drowsiness)

Receptor Equilibrium Theory

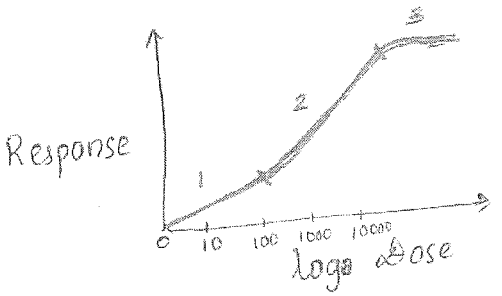
* During resting membrane potential (RMP) the receptor activators & receptor inhibitors are in equal amount. ie, in equilibrium state (no action)

50% Ra | 50% Ri
RMP

* ~~Rax~~ Full agonist → Acts on Ra
* Partial agonist → Ra >> Ri
* Antagonist → Ra = Ri
* According to this theory, no inverse agonist.

Calculation of drug action.

* With the help of log DRC (Dose Response Curve - DRC)



* 2 → Straight line (max. activity)
* Sigmoid curve
* 1 → Intial slow stage.
* 3 → Again activity falls
* Advantages of log DRC:
  1) Wide range of dose (very small distance)
  2) With the help of this curve middle part of curve is in straight line (calculation is easy) → by calculate we use straight line equation.

- Straight line equation

$mx + c = y$

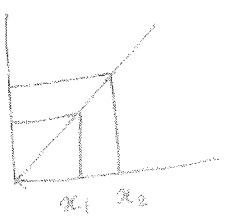
m = constant / slope of line

c → intercept at which cut y-axis

$c = 0 \Rightarrow$ ~~x~~ $mx = y$

$\therefore$ Slope $= m = y/x$.

$m = \frac{y_2 - y_1}{x_2 - x_1}$ (same everywhere)



eg: x_1 10 mg = 30 % y_1

x_2 100 mg = 70 % y_2

x_3 = 1000 mg = ?

$$m = \frac{y_2 - y_1}{x_2 - x_1}$$

$\log 10 = 1$

$$= \frac{70 - 30}{\log 100 - \log 10}$$

$$= \frac{70 - 30}{2 - 1} = 40$$

m is constant.

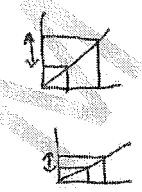
$$m = \frac{y_3}{\log 1000}$$

$$\therefore 40 = \frac{y_3}{3} \quad y_3 = 40 \times 3 = 120\%$$

* Slope is constant
* Slope shape tells about safety of drug.

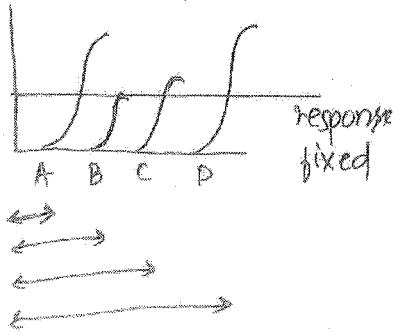
flat → safe

steap → unsafe



3) Efficacy of drug & potency of drug

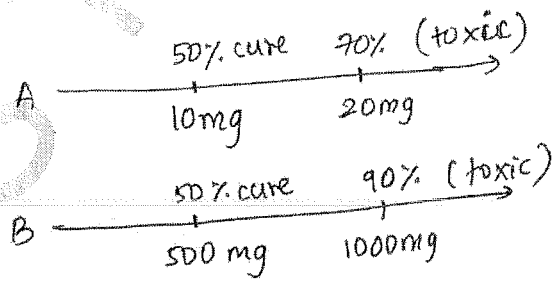
- Potency = Amount of drug required to produce a certain response
- Calculates in x-axis.



A > B > C > D

- Left side DRC → medicine is more potent
- It towards right side of DRC → medicine is less potent.
- Efficacy is maximum response produced by a drug at any given dose.
- Efficacy is calculated in y-axis
- Height of curve more important (height ↑, efficacy ↑)

D > A > C > B



Potent → A > B (amount of drug)

Efficacy → B > A (no: of patients cured)

* Efficacy is more important than potency.

4). Effective dose (animals) / Therapeutic dose (human) (SD)

(ED_{50} / TD_{50})

It is dose of drug required to produce 50% response

- Lethal dose (animals) / Toxic dose (human) (SD)

(LD_{50} / TD_{50})

Amount of dose which produce 50% death.

* eg: 10 mg = ED_{50} (10mg dose given to rates, 50% cured)
(In human it is therapeutic dose)

20 mg → 50% rat died
So LD_{50} , in human Toxic dose

* Therapeutic range → 10-20 mg
(ED_{50} → LD_{50}) (Within this range can use the drug) (no side or death)

* Therapeutic index (TI) = $\frac{LD_{50}}{ED_{50}}$

If TI > 2 → drug is safe to use

TI < 2 → drug is not safe to use.

(Because if by chance, the person takes double dose, then also it wont be lethal. So TI > 2 is safe)

* So as therapeutic index ↑↑, safety ↑
* Thus therapeutic index is an index of safety.
* Wide therapeutic index → wide difference b/w therapeutic dose & lethal dose.

eg: Paracetamol → 500 mg Thera. dose
Lethal dose : 20,000 mg (20 gm)

* Narrow therapeutic index → less difference b/w TD & LD.

* Side effect & toxicity are not same.
* Narrow therapeutic index.

1) Lithium → 0.5 - 1.4 meq/L
2) Phenytoin → 10-20 mg/ml.
3) Carbamazepine → 4-12 mg/ml
4) Phenobarbitone → 10-30 mg/ml.
5) Digoxin → 0.2-2 ng/ml.
6) Theophylline → 5-20 µg/ml

↓

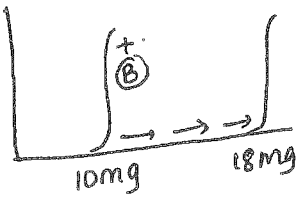
So all these medicine need strict monitoring k/a Therapeutic drug monitoring.

5) Competitive & Non competitive blocker effect.

Drug → 10 mg, produce a response

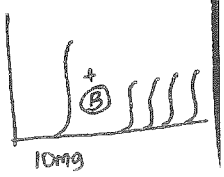
Give blocker → to it

Again give 10mg drug → no response but got response (same response) at 18 mg.



* In presence of blocker, we need higher doses to produce same response → Right curve → by competitive blocker

* But non competitive block → no response after that ↓ → flat response curve.



Metabolism

* Also k/a biotransformation
* Done in Liver > Lungs.
  (Not kidney)
* Enzymes in liver acts on drug and convert it in to inactive form
* Then it is filtered in urine & eliminated out.
* Liver enzymes are present in hepatocytes → 2 types

Phase 1 enzyme
(Non conjugative)

- Active → Inactive (more common)
- Inactive → Active (prodrug)
- Active → Active

Enzymes involved

1) Reductase enzyme (Reduction)
2) Oxidase (Oxidation)
3) Hydrolase
4) Cyclase
5) Decyclase

Phase 2 enzyme
(Conjugative)

- Only 1 possibility
  Active drug → Inactive drug

Actions involved

1) Glycine group conjugation
2) Glutathione grp C
3) Glucoronide group conjugation
4) Methyl grp C
5) Sulfate grp C
6) Nucleotide grp C
7) Acetyl grp C.

* Phase I are mainly carried by CYP450 (CY-cytochrome, P450 – wavelength of light)
* They are present on surface of sarcoplasmic reticulum.
* MC CYP450 involved in drug metabolism
  3A4 > 2D6
* In phase II → glucoronide group conjugation is the MC reaction.
* Medicines metabolized by glucoronide group conjugation:
  - C – Chloramphenicol
  - L – Lorazepam
  - A – Acetaminophen
  - M – Morphine
  - P – Pethidine.
* Acetylation → by acetyl transferase → some have high metabolism, some have slow metabolism
* If slow → slow acetylation (Indians)
* If fast → Fast Acetylation
* This variation is k/a pharmacogenetic variations.

* Medicines metamobilized by acetylation.

S - Sulfonamides
H - Hydralazine
I - Isoniazide (INH)
P - Procainamide
P - PAS (Para amino salicylic acid)
D - Dapsone.

↓

S/e: SLE like reaction

* Some of the enzymes can induce liver enzymes → induce drug metabolism
* Some others are inhibitors of liver enzyme → inhibits drug metabolism
* Liver enzyme inducers:

C - Corticosteroids
A - Antiepileptic drugs (except Sodium Valproate)
R - Rifampicin
G - Griesofulvine
A - Alcohol
S - Smoking

* Liver enzyme inhibitors are:

P - Phenylbutazone
E - Erythromycin
A - Allopurinol
C - Ciprofloxacin, Clindamycin
O - Omeprazole
C - Cimetidine
K - Ketoconazole
I - Itraconazole
S - Streptogramanins, Na valproate

Peacock - Protease Inhibitors.

Elimination (on Kidney)

* Net elimination = Amount of (I) drug filtered + Amount of drug secreted - Amount of drug reabsorbed

$$NE = F + S - R.$$

* So net elimination is amount of drug eliminated from body.
* Elimination depends on:

1) Filtration (through Bowmans capsule)

- ↑ RBF (renal blood flow) then ↑ filtration.
- ↑ ^{plasma} protein binding → ↓ filtration (size ↑)

2) Tubular secretion:

- Maximum in PCT
- With the help of 2 ATP pumps
  1) Organic anion transporter
  2) Organic cation transporter (OAT, OCT)
- OAT → are acid drugs → donates H^+ (A^-H^+)
- OCT → are basic drugs → donates OH^- (A^+OH^-)
- Can result in drug interactions
  - Diuretics + Uric acid → both have same ~~receptor~~ pump → diuretics secreted → ↑ uric acid in plasma

- Methotrexate + NSAIDS → NSAIDs eliminated → Methotrexate toxicity.
- Penicillin-G + Probanicid → probanicid eliminates → ↑ penicillin G concentration → ↑ bactericidal action

3) Tubular reabsorption :-

"Like is absorped in like medium"

- Acidic drug in acidic medium → it remains chargeless to neutralize → so no charge → get reabsorbed.
- So if acidic drug toxicity → dont want to reabsorb → so change medium to alkaline ↓
- Forced alkaline diuresis → $NaHCO_3$ inj → ROC in Barbiturate & methotrexate toxicity
- Forced acidic diuresis → NH_4Cl inj → ROC for Amphetamine toxicity

(II) Rate of Elimination:

Amount of drug eliminated from body per unit time. (mg/hr)

(III) Clearance (Plasma Clearance):

Amount of plasma cleared off drug per unit time.

Unit → mL/hr (mL of plasma)

$C_L = \frac{RE}{PC}$ (Rate of elimination / (Plasma clearance))

IV) $t_{1/2}$ (half life time).

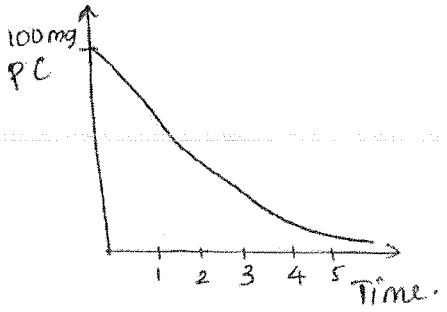
Time required to reduce drug concentration to ½ in plasma.

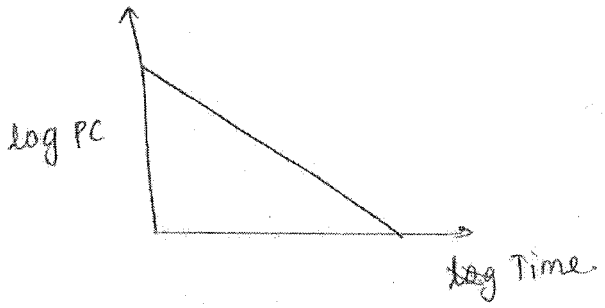
100 mg ↓ 1hr → 50 mg (50%) → 1 hr → 25 mg (25%) → 1 hr → 12.5 mg (12.5%) ↑ 1 hr → 6.25 mg (6.25%) ↑ 1 hr → 3.125 (3%)

* 95 % ≈ 100 % (drug comes out of the body)

mcq * So after 4 $t_{1/2}$ drug is completed eliminated

* Or drug remains in body for 4 $t_{1/2}$.





* Curved line → difficult to calculate → made it straight by taking log of plasma conc.

Slope (k) = Elimination constant = y/x.

* k → fraction of drug eliminated in unit time.

MUP

$$t_{1/2} = \frac{\log 2}{k}$$

$$t_{1/2} = 0.693 \times \frac{Vd}{C_L}$$

⇒ If repeat the dose of a drug after a fixed interval before the complete elimination of the previous dose, after the time period of 4 $t_{1/2}$, rate of drug entry in plasma becomes equal to rate of elimination from the body.

This state is known as steady state concentration.

↓

After this state drug concentration remain constant in patient body.

10mg ⟶ 10mg ⟶ 0mg eliminated
↓ 1hr
10 mg given ⟶ 5mg (15mg) ⟶ 5mg
↓ 1hr
10mg ⟶ 7.5mg (17.5mg) ⟶ 7.5mg
↓ 1hr
10mg ⟶ 8.75 (18.75) ⟶ 8.75mg
↓ 1hr
10mg ⟶ 9.35mg (99.35) ⟶ 9.35mg
↓ 1hr
9.7mg ⟶ 9.75mg

After 4 $t_{1/2}$ ⇒ ≃100% present in plasma ≃100% eliminated

↓

10mg ⟶ 9.7mg ⟶ 9.7
(19.7)
↓ 1hr
10 ⟶ ≃10 ⟶ 10
(20)
↓ 1hr
10 ⟶ 10 ⟶ 10
(20)
↓ 1hr
↓
(repeat)

* So after 4 $t_{1/2}$, steady state concentration is achieved.
(drug concentration remain constant in patient body)

(I)
* Loading dose & maintanence dose is used in ~~drugs of long $t_{1/2}$~~.
1) drugs with long $t_{1/2}$
2) Acute emergency

* Loading dose → It is the higher dose given to achieve desired concentration in short span of time

* Maintenance dose → It is the low dose given to maintain desired concentration in the patient body.

$$Vd = \frac{\text{Dose administration}}{\text{Plasma conc. (PC)}}$$

Loading dose = Vd × PC

(Vd - Volume of distribution)

$MD = R \cdot E$

(Maintenance dose = Rate of Elimination)

* $\boxed{MD = RE = C_L \times PC}$

$\boxed{LD = Vd \times PC}$

$$\frac{LD}{MD} = \frac{Vd}{C_L}$$

$$t_{1/2} = 0.693 \frac{Vd}{C_L}$$

$$\therefore \boxed{t_{1/2} = 0.693 \frac{LD}{MD}}$$

$$Vd = \frac{\text{Dose Adm / Loading dose}}{PC}$$

$$C_L = \frac{RE / MD}{PC}$$

$$t_{1/2} = 0.693 \times \frac{Vd}{CL}$$

$$= \log_e 2 \times \frac{Vd}{C_L}$$

$$t_{1/2} = \frac{\ln 2}{k} \quad \left(k = \frac{C_L}{Vd}\right)$$

(VI) Kinetics of Elimination:

- First order
- Zero order.

- Followed by drugs metabolized by liver enzymes present in high concentration
- By drugs metabolized by enzymes in low concentration

First order

* ↑ enzyme concentration

Ⓐ $t_{1/2} \rightarrow 1$ hr

100 mg $\xrightarrow{1hr}$ 50 — 50 mg/hr out

200 mg $\xrightarrow{1hr}$ 100 — 100 mg/hr out

500 mg $\xrightarrow{1hr}$ 250 — 250 mg/hr

1000 mg $\xrightarrow{1hr}$ 500 — 500 mg/hr

Zero order

* ↓ enzyme concentration

Ⓐ $t_{1/2}$ = 1 hr

Enzyme → 100 units.

100 mg $\xrightarrow{1hr}$ 50 mg — 50 mg/hr

200 mg $\xrightarrow{1hr}$ 150 mg — 50 mg/hr

500 mg $\xrightarrow{1hr}$ 450 mg — 50 mg/hr

1000 mg $\xrightarrow{1hr}$ 950 mg — 50 mg/hr.

First order	Zero order
* Rate of elimination is variable. RE ∝ Drug conc.	* RE = constant
* Constant fraction of drug is eliminated per unit of time. K = constant	* K is variable. $K \propto \frac{1}{\text{Drug conc.}}$
* $t_{1/2}$ = constant. $t_{1/2} \propto \frac{Vd}{C_L}$	* $t_{1/2}$ is variable. * $t_{1/2}$ ∝ drug concentration
* Vd & C_L also constant	* C_L is variable. $C_L \propto \frac{1}{\text{drug conc.}}$

* All drugs follow first order kinetics
* Zero order kinetics:

W - Warfarin
E - Ethanol
P - Phenytoin
T - Tolbutamide
T - Theophylline.

⇒ If enzyme = 100 units, then before uptill 100 mg the drug follows first order kinetics
⇒ After that it follows zero order kinetics / Saturation kinetics.

Drug Discovery

* 3 steps
  1) In silico trial
  2) Pre clinical trial
  3) Clinical trials.

~~* Approach → Target based approach~~

In silico trial

* Approach → target based approach
* Aim → To discover lead compound (most suitable compound against a given target)
* On the basis of molecular structure he will discover lead compound.

Preclinical trial

* The leading compound is tried in animals
* Animals can be rodents / rabbit
* Guinea pig is best rodent (Its physiology more similar to human)

Clinical trial

* IND (Investigational New Drug) application to FDA office (New Delhi)
* Seeking permission to start clinical trials.
* Food & Drug Administration (FDA)
* Now drug is given to human.
* 3 trials
  1) Phase I
  2) Phase II
  3) Phase III

* Phase I → drug to normal healthy
  → Sample size < 100 person
  → Calculate pharmakinetics (PK) & PD & Toxic dose (Cannot calculate pharmaceutical dose as he is not patient)
  → Non blind (he knows)
  → Head: Clinical pharmacist
  → Not done for Anticancer drugs & immunosuppressants (highly toxic)

* Phase II -
  - Sample size 100 - 200 patients
  - Calculate PK, PD, Therapeutic dose
  - Single blind (patient don't know)
  - Done by Clinicians

MCQ
  - First time drug is given to ~~human~~ patients

MCQ
  - Maximum incidence of failure

* Phase III -
  - Used in patients
  - >1000 patients
  - Calculate PK, PD, Therapeutic dose
  - Double blind (both ~~drug~~ & doctor and patient dont know. Only the one done research knows)
  - Conducted by Clinician

MCQ
  - Best phase to calculate drug potency, efficacy & to compare two drugs, less chance of error (large sample size)

⇒ After all successful phase, again NDA to FDA office → for permission to launch this medicine in market

↓

Phase IV

(Post Marketing Surveillance)

↓

Reporting of any s/e or adverse effect caused by drug, not reported previously.

Orphan Drug

* Discovered for rare disease
* For first 10 years → exclusive marketing rights / patent. (maximum profit)

eg: Antiepileptic drug → Stiripentol
↓
Dravet's disease.

GIT

Antiemetics

(1) Chemotherapy induced nausea & vomiting (CINV), Radiation induced nausea & vomiting (RINV)

- Maximum → Cisplatin
- It is a blocker of 5 HT_3 (serotonin) in CTZ (Chemo therapeutic zone) located in Area Postrema.

DOC
- eg: ~~Ondansetron~~ Ondansetron
- Palonosetron (most efficient)
- Granisetron (2nd)
- Alosetron

- MC s/e is constipation (max. Alosetron)
- Rare s/e QT interval prolongation
- Should not be given in pregnancy
- Can also use steroids Dexamethasone
- Another drug - Aprepitant

* Aprepitant → blocker of NK_1 (neurokinin - NK)
* Dronabinol (agonist of CB_1 - cannabin receptor) → reduces nausea & vomiting
* Aprepitant is antagonist of substance P.

(2) Motion sickness / Air sickness / Sea sickness
- DOC → Hyoscine (tab / skin patch)
- Also use antihistaminic drug ~~with MAO~~ → Promethazine.

(3) Morning sickness
* DOC → Doxylamine (Antihistamine) + Vit B_6

(4) Any other type of N & V
- Dopamine 2 (D_2) blockers:
  = Metoclopramide (lipid soluble)
  = Domperidone. (lipid insoluble)
- Metoclopramide → can cross BBB → blocks D_2 → causes extra pyramidal symptoms (Parkinson's like) → Also ↑ prolactin.
- So it is avoided in children.

Diarrhea

* Provide fluid therapy (Rx OC)
* If >10% weight loss → i.V fluids → best is Ringer Lactate
* If <10% weight loss → best is oral fluid - ORS
* Then nutritional therapy.
  - (continue semisolid ~~like~~ food)
  - Breast feeding should continue
* Drug therapy.
  It is according to the type of diarrhea.

1) Infective diarrhea:
- Empirical DOC → Fluroquinolone (without making a diagnosis, ie, without culture of stool & finding the organism)
- Ciplox → 500 mg BD
  Oflox → 200 mg BD
  Norflox → 400 mg BD
  Levoflox → 500 mg BD
- minimum 3 days, max - 7 days
- MC cause of diarrhea is Rotavirus (no need of drug, it will resolve itself)
- Bloody diarrhea → Dysentery By ~~Sh~~ Shigella
  - Ciplox DOC
- Rice water → Cholera
  * DOC - Doxycyclin
  * Pregnant / Child < 7-8 yr Azithromycin
- Tenesmus (involuntary anorectal contraction)
  * Suspect amoeba
  * Metronidazole group

2) Non infective diarrhea
- Due to diabetes mellitus, drug, chemotherapy, stress
- DOC: Opioids
  - Loperamide [reduces peristalsis - Antimotility] (2mg x BDS)
- Then clonidine (α_2 ↑↑) (α_2 agonist)
- Atropine (anticholinergic)

3) Secretory diarrhea:
* Octreotide is the DOC (Somatostatin analogue) ↓ Body hormone inhibitor (GI hormones also inhibited)
* Bismuth subsalicylate (NSAID)
  - Inhibitor of prostaglandin → no vasodilation in small intestine → ↓ secretions.
* Zinc
  - Reduces secretions
  - Given to all paediatric patients x 14 days
  - ~~<5m~~ < 6 month age 10 mg/day
  - > 6 month → 20 mg/day
  - s/e: Nausea & Vomiting

4) Traveller's diarrhea:
* Secretions ↑ due to change in food suddenly
* Also due to food with bacteria (infection)
* For ↑ secretion → Rx: Bismuth
* Infection → DOC: Rifampicin

Constipation

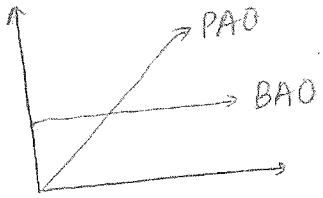
* MC type is functional constipation (↑ age → ↓ peristalsis, or physical inactivity)
* Rx Oc → Diet modification (rich in fibers)
* DOC → Ispaghula (herbal drug)
* Stimulant purgatives (stool softners)
  - Most effecient
  - Sodium picosulfate
  - Bisacodyl
  - But has abuse potential in GIT (no peristalsis without it)
  - C/I in pregnant (stimulate uterus → abortion)
* Osmotic purgatives
  - ↑ H_2O content
  - Lactulose (intermediate property)
  - Intestinal flora releases NH_3 → lactulose removes this NH_3 → best gut sterilising drug
  - So DOC for hyperammonemia is Lactulose.
  - Rifaximin → best to kill the intestinal flora (bacteria)

Irritable bowel syndrome (IBS)

* Diarrhea due to emotional instability (or constipation)
* DOC is SSRI (emotion)
* Diarrhea here → Alosteron ($5HT_3$ ⊗) (Antimotility)
* Constipation → Acts on $5HT_4$ ↑↑ → ↑ peristalsis → Cisapride, Mosapride
* Also lubiprostone, linaclotide (not important → 2 drugs)

Peptic Ulcer Disease

* ↑↑ acid production → ulceration of gastric mucosa. (duodenum → duodenal ulcer).
* Acid is produced by H^+K^+ ATPase pump → present in parietal cells/ mucosal cells.
* Stimulus of pump → 1) Histamine → H_2 → ↑ acid
  2) Gastrin → CCK_2 → H^+K^+ ATPase
  3) Vagus → Ach → M_3/M_1 (R) → H^+K^+ ATPase → acid product^n
* 2 types of acid production.
  1) PAO (Peak acid output)
     - After meal (high amount needed)
     - ↑ Fe, Ca, Vit B_{12} require acid medium for absorption
  2) BAO (Basal Acid Output)
     - 24 hrs
     - Acts as a defense mechanism (gastric mucosa)



Medicines

1) PPI : Proton pump inhibitors
   * MOA → H^+K^+ ATPase (K) (Non competitive inhibitor)
     ↓
     ↓ PAO & ↓ BAO
     ↓
     Most efficient drugs to reduce acid output.
   * Indications are:
     1) DOC for all type of peptic ulcer disease
        ↓
        except stress induced ulcer (↑ BAO) ← H_2 (K) receptor → DOC
     2) DOC in GERD (Gastro esophageal reflex disease)
        - GERD → ↓ acid product^n or ↑ food motility (Rx)
     3) DOC for ZES (Zollinger Ellison syndrome) ↑ gastrin product^n

- ↓ gastrin production by
  ↓ Octreotide (somatostatin analogue)
  (given parenteral) i.v / s.c

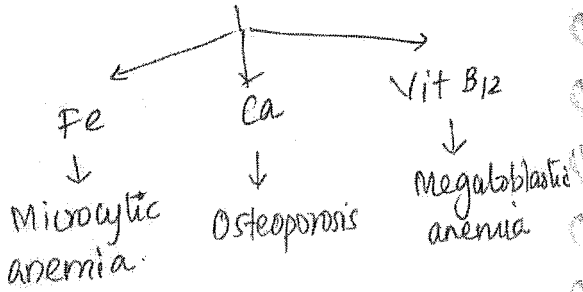
■ Pharmacokinetics

* All → oral route
  But i.v → Pentoprazole, Rabeprazole, Esomeprazole
* If given after meal → ↓ absorption
  So given before meal
* Acid sensitive → so given with enteric coating.
* Absorbed from small intestine.
  - Enteric means small intestine → alkaline media
  - In alkaline media → enteric coating dissolves.
* Liver enzyme ↓↓ (CYP2C19)
  - Max. enzyme inhibition is done by Omeprazole (of CYP2C19)
  - Omeprazole > Lansoprazole > Rabeprazole.
* Action will be from vasular side (hepatic vein → IVC → gastric artery → mucosal cell)
  30–45 min
* They will inhibit proton pump in open state (ie, when eat food)
* So they are best to be consumed 30–45 minutes before meal.
* Mucosal cell → life span 2-3 days → new mucosal cell → new proton pump → inhibited when again drug is given.
  So action of PPI lasts for 2–3 days.
* t½ of PPI → 1–4 hrs

⇓

This phenomenon is k/a Hit & Run phenomenon
(action lasts for 2-3 days but t½ of drug is 1-4 hrs)

* Efficiency:
  Tenatoprazole > Esomeprazole > Rabeprazole.
* Not safe in pregnancy & in children
  Lansoprazole can be used.
* S/e:
  1) PAO → Nutrients ↓.



  2) BAO → Defence ↓↓
  So 2° infection.

* Develops 2° infections like Pseudo membranous colitis (Clostridium Difficile)

* Aspiration of bacteria (from GIT to respiratory tract) → LRTI (lower resp. tract infections) MCQ

3) ↓ Acid production for long duration → as a reflex mechanism - proliferation of G-cells starts → leads to gastrinoma MCQ

(Medicines)

[2] H_2 receptor ~~x~~ blocker

* ↓ BAO → DOC : Stress ulcer (ICU, chronic illness, burn, mental stress)

* Indication same as PPI.

* S/e → same as PPI (↓ BAO → ↓ defense)

eg: Famotidine (most efficient)
Cimetidine
Ranitidine
Nizatidine

* Cimetidine → causes CNS toxicity (seizures), liver enzyme (CYP2C19)↓ estrogen ↑ (estrogen is metabolised by CYP in liver → ↓ CYP-↑ estro) (gynaecomastia, erectile dysfunction)
Also fetopathic (placenta)

* Nizatidine, Famotidine, Ranitidine → no s/e → Safe in pregnancy.

[3] Antacids

* Highly alkaline in nature.
* Directly neutralised in acidic media. (acts in lumen) MCQ
* Fastest acting drug in peptic ulcer disease. MCQ
* No systemic absorption
* So no systemic s/e MCQ
* Safest in pregnancy
* Disadvantage → Action is very short (30-45 min) MCQ

eg:- $Al(OH)_3 + Mg(OH)_2$ (mostly used)
Gelusil
- Megaldrate

* $Al(OH)_3$ → causes constipation alone
$Mg(OH)_2$ alone → cause diarrhea MCQ
* When combined → no s/e MCQ

[4] Antibiotics

* Against H. pylori
* Triple regimen × 14 days BD (CAMP)
↓
- Clarithromycin
- Amoxicillin/Metronidazole
- PPI

* Given for PPI resistant peptic ulcer disease.

* Quadruple regimen → outdated (TOMB)
  - Tetracyclin
  - Omeprazole
  - Metronidazole
  - Bismuth (CBS - Colloidal bismuth subcitrate)

* s/e & toxicity with bismuth → so outdated now.

5 Anticholinergic drugs:

* M_1 blockers
* Pirenzipine, Telenzipine
* Low efficiency → so outdated

6 Prostaglandin analogues:

* PGE_1 (Misoprostol) (oral)
* Misoprostol acts on GI mucosa ↔ vasodilation → ↑ secretion of mucous & HCO_3^- on surface of mucosal cells.
* s/e → Abdominal pain, nausea & vomiting, diarrhea, abortion ↓ due to s/e now outdated.
* If pregnant lady taken this → baby born with Mobius syndrome → CN 6 & 7 palsy → teratogenic effect)
* MTP → Misoprostol + Mifepristone (RU 486)

(MTP: Medical termination of ~~per~~ pregnancy)

7 Ulcer protective drugs:

- CBS (Colloidal bismuth subcitrate)
- Sucralfate (30-45 min)
- Both oral → when comes to acidic medium → gelatinous layer over the ulcer.
- They need acidic media, so cannot be given along with Antacids.
- s/e → Permanent blackening of tongue.

GERD

* Gastro oesophageal reflex disease.

1) ↓ Acid production
   - DOC → PPI
   - H_2 blocker

2) ↑ peristalsis → Prokinetic drugs
   - MOA: $5HT_4$ TT (wall of small intestine) ↓ ↓ peristalsis.

eg: Cisapride → Outdated bcoz of s/e
Mosapride
Itopride
Tegaserod
Levosulpride
Domperidone } D_2 ⊗
Metoclopramide }

* s/e of Cisapride → Cardiac conduction defects, QT prolongation, Arrythmia (TDP)

[TDP → Torsades De Pointes]

MCQ
* Cisapride → metabolized by CYP 3A4 enzyme.

MCQ
* Cisapride outdated due to s/e arrythmia

3) Macrolide Antibiotics

* MOA: ↑↑ motilin receptors (M) in small intestine

* Erythromycin → Used for GERD, Constipation, gastroparesis

CNS

Antiepileptic drugs

* Epilepsy → have seizures due to overactivity of neurons

■ Classification:

1) Na^+ channel blockers

* Sodium Valproate, Carbamazepine (CBz), Oxcarbamezepine, Phenytoin, Fosphenytoin, Topiramate, Lamotrigine, Rufinamide.

2) Calcium channel blocker (T-type Ca channel)

* Sodium Valproate
* Topiramate
* Lamotrigine
* Zonisamide
* Ethosuximide

3) K^+ channel openers

* Ezogabine

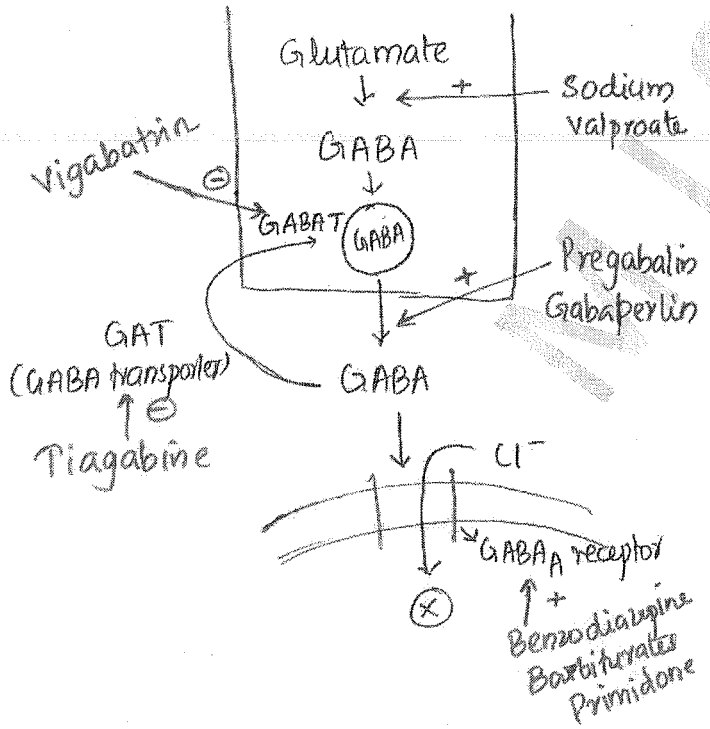
4) Glutamate pathway ~~blockers~~ inhibitors

* Glutamate - Excitatory
* Glutamate acts on 3 type of receptors
  - ~~NM~~ NMDA
  - AMDA
  - Kainate

* Levitiracetam → blocker of vesicular protein 2A (SynV2A) (acts at vesicle)
* Glutamate release inhibited by Lamotrigine
* Blocker of receptors
  - NMDA → Sodium Valproate, Felbamate
  - AMDA → Felbamate
  - Kainate → Topiramate.

5) GABA pathway enhancer

GABA : Inhibitory



* GABA reuptake by GAT
* Then acts by GABA transaminase & metabolize it

* Sodium Valproate → ↑ GABA path
* ↑ GABA release
  - Pregabalin
  - Gabaperlin.
* Inhibit GABA transporter
  - Tiagabine
* Inhibit GABA transaminase
  Vigabatrin.
* Stimulate GABA$_A$ receptor
  - Benzodiazepine
  - Barbiturates.
  - Primidone

Indications of Antiepileptic drugs

1) Generalised Epilepsy
(All lobes of brain are involved)

a) GTCS (Generalised tonic clonic seizures)
- Present in adult (Grand Mal)

b) Absence seizures
(all lobes involved, but no body movements)
- Present in children (Petit mal)

c) Myoclonic seizures

d) Atonic seizures

⇒ DOC for all this 4 types is Sodium Valproate > Lamotrigine.

2) Partial / Focal seizures
(Only one or two lobes involved)

* So less severe seizure.
* If loss of consciousness → complex partial
* No loss of consciousness
Simple partial
* DOC for both:
Oxcarbamezipine > Carbamezipine

3) Pregnant

* Seizures because of Eclampsia
DOC → $MgSO_4$
* Monitor 3 parameter
1)
2)
3)

* Non Eclampsia:
  - Safe → Lamotrigine > Oxcarbamezipine > Carbamezipine.
  - Unsafe → Sodium valproate > Phenytoin.

4) Childhood seizures

a) Febrile seizures (fever) — seizure occurs when
- DOC → Diazepam (I.m / rectal)
- So to prevent it → prevent fever → Prophylaxis: Paracetamol

b) Infantile spasm (Salaam seizure)
- Abdominal muscle spasm (so he bend forwards)
- Basic problem is hormone imbalance
- DOC → ACTH / CRH
- If ACTH resistant infantile spasm
  - DOC → Vigabatrin
  - S/e is loss of vision (retinal damage → leads to blindness)

c) Absence seizures
- Generalised type
- Ca^{2+} T-type channels involved
- So Ca^{2+} TC ⊗ used
DOC → Sodium valproate

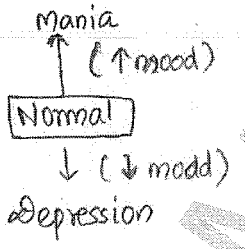
d) Subtle seizures
- MC type of childhood seizure
- DOC → Phenobarbitone

5) Status Epilepticus

* Continous seizures for 5-10 min
* Or present intermittenly for 30-45 min without regain of consciousness in b/w.
* Life threatening → I.V
* DOC → Lorazepam > Diazepam > Midazolam > Clonazepam (nasal spray)

Sodium Valproate

- MOA: Na^+ ⊗, Ca^{2+} ⊗, NB NMD receptor ⊗, ↑ GABA synthesis.
- Indications:
  (1) Epilepsy
  - DOC → Generalised epilepsy
  (2) Rx. of neuralgia (Na⁺ ⊗, so blocks sensory nerves)
  (3) Rx. of migraine prophylaxis (Ca^{2+} T-type ⊗)
  - Vasodilation → migraine → trigeminal ganglia is involved.
  (4) Used in bipolar disorders.



  - Any drug given for bipolar disorder → Mood stabiliser
  - Sodium Valproate: DOC for acute mania.
- Pharmacokinetics (PK):
  * All CNS drugs are lipid soluble.
  * All CN drugs are metabolized by liver except lithium (kidney)
  * All CNS drugs are acidic drugs (binds to albumin) except lithium → Not protein bound.

* All important antiepileptic drugs are liver enzyme inducer ~~except~~ (CYP 450 ↑↑) except sodium valproate (CYP 450 ↓↓) (inhibitor)

- S/e:
  * All antiepileptic drugs causes MC s/e – Sedation & Drowsiness.
  * All antiepileptic drugs when given in high dose → Cerebellar toxicity (Ataxia, Nystagmus)
  * Other s/e of sodium valproate is
    W → Weight gain (maximum)
    H → Hormonal imbalance (♀ > ♂)(PCOD)
    A → Alopecia
    T → Tremors
    A → Ataxia (↑↑dose)
    P → Pancreatitis
    L → Liver toxicity (severe)
    A → ↑ NH_3 (Ammonia)
    N → Neural tube defect (Teratogenic) (Spina bifida)

Carbamezapine (CBZ)

- MOA → Na^+ ⊗
- Indications:
  1) Epilepsy → DOC: Partial seizures
  2) Neuralgia → Na^+ ⊗
     DOC: Trigeminal Neuralgia.

3) Bipolar disorders (Mania)

■ PK:

* Same like sodium valproate
* CBZ $\xrightarrow[\text{liver}]{CYP3A4}$ Metabolite ↓ s/e: Bone marrow suppression.

■ S/E:

1) Bone marrow suppression
2) Mild liver toxicity
3) Water retension (SIADH → Syndrome of inappropriate diuretic hormone) (↑H_2O → ↓Na^+ hyponatremia)
4) SLE like symptoms.

Phenytoin

■ MOA → Na^+ ⊗

■ Indication:

1) Rx. of epilepsy
2) Neuralgia
3) Na^+ ⊗ in heart muscle → ↓HR So given in Arrythmia.

■ PK:

1) ROA → Oral
   * Fosphenytoin (liquid) → i.v (for status epilepticus)
2) Absorption: Different brands of phenytoin has different absorption pattern → k/a Bioinequivalent.
3) Distribution: Narrow therapeutic index.
   * So requires therapeutic drug monitoring.
   * Concentration of phenytoin in plasma should be 10-20 µg/ml.
   * Can cross placenta → fetal hydantoin syndrome. (baby born with hypoplastic phalanges - upper limb fingers will not develop).
4) Metabolism: By liver (zero order kinetics)

■ S/E:

- Sedation & Drowsiness
- ↑ dose → Cerebellar toxicity
- Fibrosis everywhere in body (Gum hypertrophy, acne, pseudolymphoma - in body, fibrotic deposition appears like lymph node)
- ↓↓ Vitamin (↓D, K, folic acid)
  - ↓D - Osteomalacia
  - ↓K - Bleeding
  - ↓folic acid - megaloblastic anemia.
- Hypertrichosis (hirsuitsm)
- ↓ Insulin release (hyperglycemia)

Topiramate

- MOA : Na^+ ⊗, Ca^{2+} ⊗, kainate receptor ⊗
- Indication :
  1) Epilepsy
  2) Neuralgia (Na^+ ⊗)
  3) Migraine (Ca^{2+} ⊗)
  4) Weight loss (Obesity)
  5) Tremors (M-receptor ⊗)
- s/e :
  1) Weight loss (maximum)
  2) Muscarinic ⊗ → Dry mouth, dry eyes, mydriasis (precipitate glaucoma), constipation, hypohidrosis (↓ sweating)
  3) Carbonic Anhydrase ⊗ → HCO_3^- loss → Metabolic acidosis → urine - alkaline (HCO_3^- loss) → Ca^{2+} precipitate in alkaline urine and causes renal stones.

Lamotrigine

- MOA : Na^+ ⊗, Ca^{2+} ⊗, glutamate release ⊗
- Indication :
  1) Epilepsy
  2) Safe in pregnancy as anti epileptic
  3) Neuralgia
  4) Migraine
  5) Bipolar disorder (Depression)

  Lamotrigine is the only antiepileptic used in bipolar disorder.
- s/e:
  * Hypersensitivity
    - Mild → skin rash
    - Severe → Steven-Johns syndrome.

Benzodiazepines

- MOA : $GABA_A$ ↑↑
- Indication
  1) Epilepsy
     - Diazepam : DOC in febrile seizure
     - Lorazepam : DOC in status epilepticus.
     - ~~Metronidazole~~ : Midazolam (Nasal spray)
     - Clonazepam (Absence seizure)
  2) Insomnia :
     - DOC for acute insomnia
     - Alprazolam, Diazepam, Lorazepam.
  3) Antianxiety property
     - DOC for acute anxiety.
  4) Pre-anesthetic medication
     ↓ anxiety & ↑ sleep.

5) DOC for alcohol withdrawal syndrome.
Chlordiazepoxide.

6) Muscle relaxant → Diazepam.

■ PK:

* Wide therapeutic index (safe) (So toxicity is not common)
* Metabolized by liver.
* All are liver enzyme inducers. (mild inducer) (So drug interaction is uncommon).
* $t_{1/2}$ >>> (long acting) → s/e: Hangover

Except → Midazolam, Triazolam, Temezepam, Estazolam (short acting)

■ s/e

1) Inhibit respiratory centre → ↓RR
2) Inhibit vasomotor centre → ↓ BR, ↓ HR
3) ↓ acid production in GIT
4) $t_{1/2}$ >>> → Hangover
5) ↓ Anxiety → Addiction.
6) Long duration Rx (modify sleep pattern)
↓
Prolong phase II in NREM. (So ↓ duration of phase I, III, IV, REM) (IV - deep sleep → so no deep sleep here)

Toxicity of Benzodiazepines

* It is rare
* Death occurs due to ↓RR, ↓ VMC (vaso motor centre)
* Antidote → Flumazenil (i.v) (competitive inhibitor of benzodiazepines)

Barbiturates

■ MOA → $GABA_A$ ↑↑↑

■ Indications:

1) Epilepsy → Phenobarbitone (DOC for subtle seizures)
2) Thiopentone sodium → General Anesthesia.

■ PK:

1) Narrow therapeutic index So need therapeutic drug monitoring.
Phenobarbitone → 10-30 µg/ml
2) Liver (metabolise in)
3) Liver enzyme ↑↑ (strong inducer)
++ Drug interaction. (CYP 450)
4) Liver enzyme → ALA synthase ↑↑ (precipitate porphyrias) → acute intermittant prophylaxis

* Known case of porphyria, Phenobarbitone is C/I

5) $t_{1/2}$ → Phenobarbitone $t_{1/2}$ >>>
→ Thiopentone Na $t_{1/2}$ <<< (inducing agent) in anesthesia

■ S/e :
* MOA same as benzodiazepine
* So s/e also same.
* More efficient than benzodiazepines so all s/e also more severe than benzodiazepine.

■ Toxicity
* More common
* ↓RR, ↓VMC
* No antidote
* Rx OC → forced alkaline diuresis.

Pregabalin & Gabapentin

■ MOA : ↑↑ release of GABA
■ Indications –
1) Epilepsy
2) Neuralgia (DOC for all type except trigeminal neuralgia
3) (P > G)

DOC for Trigeminal N is Carbamazepine.

3) Migraine

→ Antiepileptic used in Migraine
1) Sodium valproate
2) Topiramate
3) Lamotrigine
4) Pregabaline
5) Gabapentin

Sedatives & Hypnotics

* Used to Rx Insomnia
* 1) $GABA_A$ ↑↑
* Benzodiazepine (BZD) & Z drugs

Benzodiazepine	Z drugs
Alprazolam	Zolpidem
Diazepam	Zopiclone
Lorazepam	Zaleplone

* BZD >>> Z drugs (efficient)
* Same PK, MOA, s/e, antidote
* ~~But all BZD >> Z drug~~
* BZD has more s/e.

2) Melatonin receptor agonist :
Can act on 2 receptors.
i) MT_1 → Induce sleep
ii) MT_2 → Maintain sleep cycle.

* So used in insomnia, jet lag, old patients, blind, depression person

* Ramelteon
* Agomelatine
} Melatonin agonist

↓

Rare s/e: Hormonal imbalance.

Psychiatry

1) Psychotic disorders (Psychosis)
   * Insight absent
   * Complaince is very poor
   * eg: Psychotic disorders:
     - Mania
     - Schizophrenia
     - Delusional disorders
   * High dopamine level, serotonin also high in some patients.
   * Mesolimbic pathway → ventral tegmental area → Dopamine is released → acts on D_2 ® → Euphoria.
   * Mesocortical pathway → from cortex → Dopamine release → D_2 receptor → Cognition (awareness)

Antipsychotics

- Typical
  - ↓
  - MOA: Blocks dopamine receptor
- Atypical
  - ↓

Typical

* MOA → D_2 receptor ⊗
* Indication:
  1) DOC in psychosis (mania, schizophrenia, delusion)
  2) Safe in pregnancy (DOC)
  3) Post partum psychosis (DOC)
  4) Gilles de La Tourrette (DOC) (Tic syndrome - excessive contraction of orofacial muscle)
  5) Refractory hiccups (DOC)
  6) D_2 ⊗ → Antiemetic (Rx - Nausea & Vomiting)

* PK:
  - Lipid soluble, acidic, combines to albumin,
  - Metabolized by liver.
  - Most potent: ~~Atlop~~ Haloperidol
  - Minimum: Chlorpromazine, Thioridazone.
  - ROA: MC-Oral, also depot injection (long acting preparation)
    → Haloperidol, Fluphenazine.
  - s/e: DHAM
    - D_2 ⊗ → Parkinson's like symptom / Extrapyramidal symptom, ↑ prolactin
    - Histamine ⊗ → Sedation and drowsiness,

↑ appetite (weight gain)

- α_1 ⊗ → ↓ BP
- M ⊗ → Dryness, constipation, mydriasis, ↑HR (rarely ~~RDR~~ TDP

⇒ ~~minimum~~ ~~Maximum~~ ~~D_2 ⊗~~

~~Chlorpromazine > Thioperi~~

⇒ ~~Maximum D_2 ⊗~~

s/e (Full mcq)

* Maximum D_2 ⊗ s/e → Haloperidol
* Minimum D_2 ⊗ s/e → Chlorpromazine > Thioridazole
* Maximum H_1 & α_1 ⊗ s/e Chlorpromazine > Thioridazole
* Minimum H_1 & α_1 ⊗ s/e Haloperidol.
* Maximum M ⊗ s/e Thioridazole > Chlorpromazine
* Minimum M ⊗ s/e Haloperidol

* Other s/e
  - Chlorpromazine → Cholestatic jaundice
  - Thioridazole → Retinal degeneration (Brown vision)

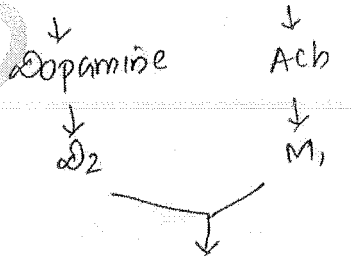
* Rare s/e of antipsychotic: Neuroleptic malignant syndrome ↑ (genetic disorder)

- D_2 ⊗ → Hyperthermia, HTN, ↑HR, Amythmia, Seizures, Vasospasm.
- DOC for neuroleptic malignant syndrome is Bromocriptine (i.v)

Types of Extrapyramidal ~~syndrome~~ symptom

1) Acute muscle dystonia (AMD)
2) Drug induced Parkinsonism (DIP)
3) Akathesia

⇒ Nigrostriatal Pathway (involves substantia nigra)



* When antipsychotics (D_2 ⊗) given to nigrostriatal pathway → It affects body movements.
* Acute muscle dystonia (AMD)

1) AMD

~~D_2 DR~~ ~~→ 3-4 wks~~

→ 3-4 days
→ MC: sternocleido mastoid.
(Bending of neck to one side)
↓
Torticollis

* Severe → Eye ball movements (abnormal)
(extra ocular muscles)
↓
Oculogyric crisis

* Rx : stop typical antipsychotics
start atypical antipsychotics
↓
Clozapine.

2) ∅IP

* 3-4 wks
* Same symptom like Parkinsonism
  - Rigidity
  - Tremor (most prominent)
  - Mask like face
  - Bradykinesia

* Rx. with M_1 ⊗
∅OC: Benzhexol (Trihexyphenydyl)
Benztropine.

(2) H_1 ⊗ & M_1 ⊗
Promethazine.

Imp EPS

AMD	DIP	Akathesia	TD
4 day	4 wk	4 mon	4 yr
- scm	- PD	- Restless	- Tics
- eom	Benzhexol	Propranolol	- Dyski (Rabbit)
- ∅OC: Benzhexol			↓ - stop typical - Clozapine

3) Akathesia

* 3-4 months (s/e appear)
* "Inner A' Restlessness", reason not known
* ∅OC : β_2 ⊗ Propranolol

4) Tardive Dyskinesia

* s/e appears after 3-4 yrs
* Tics (Rabbit syndrome) or (Hare syndrome)
* Painful body movements
* D_2 ⊗ for long duration → counter action of body → upregulation of D_2 receptors (major problem)

Atypical Antipsychotics

* MOA : 5HT pathway ⊗ >> Dopamine pathway ⊗

* s/e: DHAMS
  - D_2 ⊗ — Risperidone (max) — Clozapine > Olanzapine (min)
  - H_1 ⊗
  - α_1 ⊗ — Clozapine > Olanzapine — Aripiprazole
  - M ⊗
  - S — seizures, sexual dysfunction

Clozapine

* Most preferred drug for
  a) Refractory ~~causes of~~ cases of psychosis
  b) Psychosis c poor prognosis
  c) Psychosis c suicidal tendency
  d) Psychosis c Tardive dyskinesia c typical drugs.

MCQ
* s/e : DHAMS + Myocarditis + Bonemarrow suppression
  (All severe s/e) (stop drug)

MCQ
* MC s/e is Sedation / Drowsiness
* Then weight gain (Diabetes mellitus)

MCQ • ↑ salivation (here only)

* Used as depot form (injection)
  Risperidone, Aripiprazole, Paliperidone.

⇒ Quetiapine.
  s/e → Cataract

⇒ Atypical antipsychotics (Mood stabilisers)
  BPD (mania + Depression)

Neurotic disorder

* Insight present
* Good complaince
* Includes depression & anxiety disorder.

* Anxiety disorders:
  1) OCD (Obsessive Compulsive Disorder)
  2) Phobia
  3) PTSD (Post traumatic stress disorder)
  4) Panic
  5) Bulimia Nervosa
  6) Generalised Anxiety disorders.

Pathophysiology

+ ↓ 5HT (serotonin) >>> ↓ NAdr

Antidepressant

Typical ← → Atypical

Typical

1) SSRI → SERT ⊗

Typical

① * SSRI → SERT ⊗ → ↑ 5HT

* Indication
  1) DOC for depression
  2) DOC for anxiety disorder
  3) DOC for fibromyalgia (Non specific migratory pain)
  4) DOC in irritative bowel syndrome.
  5) DOC in premenstrual ~~mood~~ symptoms.
  6) DOC for vasomotor symptoms of menopause.
     Rx OC → Hormone replacement therapy.
     (Estrogen) + (Progestens)

7) Pre-mature ejaculation :- DOC
(Nomal : 5-20 minutes)

PK

* Metabolized by liver
* Fluoxetine → longest acting SSRI, MCQ & max. protein binding, liver enzyme inhibitor.
* Paroxetine :
  - Shortest acting ($t_{1/2}$ <<<)
  - Most efficient
  - Most non specific SSRI (so maximum s/e)
* Fluvoxamine :
  - 2nd shortest acting SSRI
* Other SSRIs :
  - Escitalopram - Most specific with minimum s/e. But least efficient.
  - Sertraline (Que : Sertraline belongs to ? SSRI)

S/e of SSRI

1) * Nausea & Vomiting (most common)
(↑5HT → 5HT3 ® ↑)
2) * Diarrhea
(↑5HT → 5HT4 ↑↑ → ↑ peristalsis)
3) * Delayed ejaculation.
4) * Blocks H_1 → Sedation & Drowsiness
Weight gain.
5) * Teratogenic → baby born with ~~HTN~~, pulmonary HTN, congenital heart disease

⇒ These s/e maximum - Paroxetin
minimum - Escitalopram.

6) Discontinuation syndrome (Abrupt withdrawal)
↓
Rebound depression.
⇓
Maximum - Paroxetine ($\uparrow t_{1/2}$)
minimum - Fluoxetine ($\downarrow t_{1/2}$)

7) Fluoxetine → given for initial few days of therapy → it precipitate anxiety syndromes.

⇒ DOC for anxiety & depression in pregnant females is TCA.

Toxicity of SSRI

* ↑↑ 5HT → ↑ 5HT2 receptor
↓
Neuroleptic malignant symptoms.
(Serotonin syndrome)
↓
DOC: Cyproheptadine (iv)
(5HT2 ⊗)

2) ~~SNRIs~~ TCA

* Blocks 5HT reuptake by SERT ⊗, NorAdr. ↑ (NAdr > 5HT)
by NAT ⊗

↑5HT
↓
* Indication same like SSRI except premature ejaculation.

NAdr ↑
↓ (Indication) (DOC)
* Neuralgia } Amitryptiline & Nortryptiline.
* Migraine }
* α_1 ↑ → ↑ tone of bladder sphincter
So used for Rx. of urinary incontenence, Noctumal enuresis
DOC: Imipramine

PK (of ~~SNRI~~ TCA)
* metabolised by liver
* Normal therapeutic index → therapeutic drug monitoring.

* S/e:

	Max	Min
H → H_1 ⊗ } A → α_1 ⊗ }	Doxepine	Nortryptiline Desipramine
M → M ⊗ – Amitryptiline		»

S ↗ Seizures
↘ Sexual dysfunction

Amoxapine
* s/e – HAMS + D_2 ⊗ < Extrapyramidal s/e, ↑ prolactin.

Only TCA ~~Only~~ antidepressant ~~medicine~~ with D_2 ⊗ & antipsychotic property

Toxicity of TCA
* Death → metabolic acidosis
* DOC → $NaHCO_3$.

3) SNRI
* They can ↑ 5HT & ↑ NAdr equally.
* NAdr → used in Rx. of
- Neuralgia
- Bladder
DOC: Duloxetine.
- Migraine → Venlafexine.
* 5HT → Rx. of fibromyalgia
DOC: Milnacipram.

* S/e:

↑5HT
- $5HT_2$ → Serotonin syndrome
- $5HT_3$ → Nausea & Vomiting
- $5HT_4$ → Diarrhea.

↑NAdr
- CNS → Insomnia, Wt. loss (inhibit appetite centre)
- Periphery → HTN, Tachycardia.

4) Selective Nor Adrenaline Reuptake Inhibitor

* Reboxetine

5) MAO Inhibitors (↑ NAdr)

- Selective
  - MAO-A ⊗ → Meclobamine → Rx. of Depression
  - MAO-B ⊗ → Selegiline, Rasagiline → Rx. of
    - ↑ NAdr — Depression
    - ↑ DA — Parkinson's disease
- Non-selective → MAO A & B ⊗

Non Selective
MAO- A & B ⊗
↓
Phenelzine
Tranylcypromine
↓
Rx. of depression.

* SE → H_1 ⊗
  - Sedation & (MC) Drowsiness
  - Weight gain

* MAOI + Tyramine food products
↓
Produce HTN crisis (Cheese Reaction)
↓
DOC: Phentolamine.

Atypical antidepressants

* Trazodone → Rx. of erectile dysfunction.
* Bupropion → Rx. of smoking de-addiction.
* Atomexitine → ADHD
* Mianserine
* Mirtazipine
* Tianeptine

ADHD → Attention Deficit hyperactivity Disorder.

Anti Anxiety

* For Anxiety Disorder.

1) GABA A ↑↑ → Benzodiazepine
   - Fastest acting
   - DOC for acute anxiety

2) Antidepressant → ↑5HT
   - SSRI, TCA, SNRI
   - Slow onset of action
   - DOC for maintainence Rx. (SSRI - mainly)

3) $5HT_{1A}$ ↑↑
   - Slow onset of action
   - Used for maintainence of anxiety
   - Buspirone, Gepirone

Bipolar Disorders

* Have symptoms of mania & depression.

Mood stabiliser

1) Lithium carbonate.
2) Antiepileptic drugs (Sodium valproate, Carbamezipine ⟷ Mania.
   Lamotrigine ⟶ Depression)
3) Atypical antipsychatics (mania + depression)
4) SSRIs (Depression)

Lithium carbonate

Indication:

* DOC for maintanence Rx. for bipolar disorder (slow onset)
* Neuralgia (Cluster Headache)
* SIADH (⊗ ADH in kidney)
* Myelosuppression (stimulates stem cells)

PK

* ROA: Oral
* Absorption - good, body cannot differentiate b/w Na^+ & lithium
* Distribution → Plasma
  - Narrow therapeutic index
  - 0.5 - 1.4 meq/L
  - TDM
- Can cross placenta → baby born with Ebstein's anomaly → defect in ~~side~~ right side of heart & tricuspid valve.
- Not protein bound → so hemodialysis is possible only for lithium
  ∴ Rx Oc for lithium toxicity Hemodialysis.
- Eliminated by kidney (Only lithium → by kidney)
- s/e:

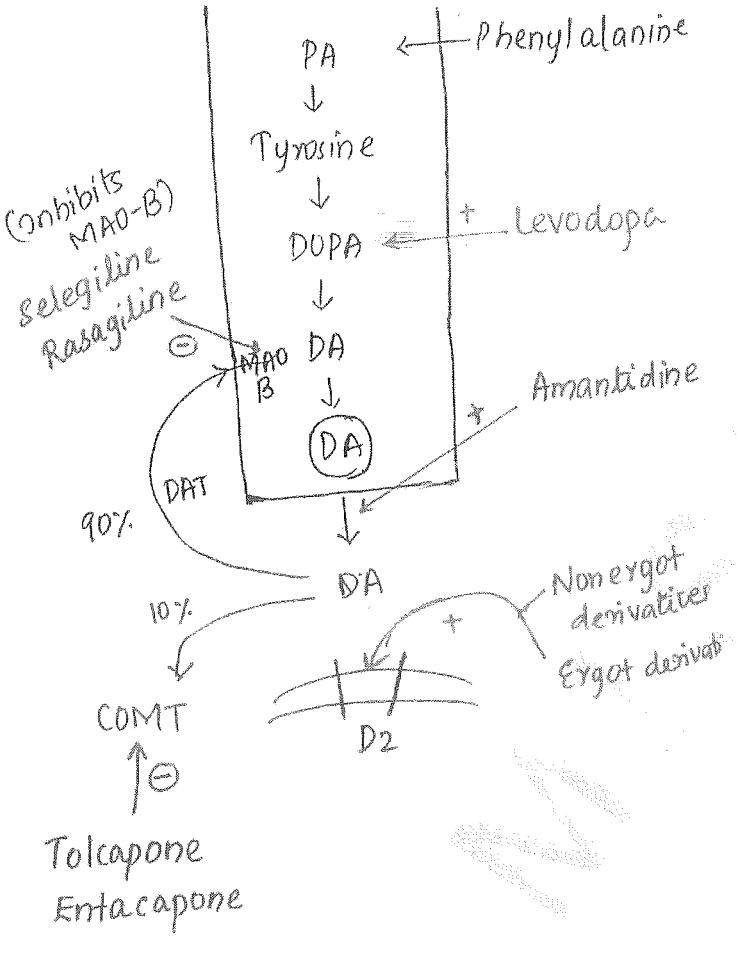
  F - Folliculitis (2nd MC)
  L - Leukocytosis (↑ WBC)
  A - Acne (2nd MC)
  T - Tremors (fine) (MC)
  toxicity → coarse tremors
  T - ↓ T3
  P - Polyuria (↑ urine output)
  A - Alopecia
  W - Weight gain

  Also ECG variations (inversion of T-waves)

Neurodegenerative Disorders

1) Parkinson's disease:

* Dopamine deficiency (Substantia Nigra)



* Ergot derivatives are:
  - Bromocriptine
  - Cabergoline
  - Pergolide

* Non-ergot derivatives:
  - Rotigotine
  - Ropinirole
  - Pramipexole

* Tolcapone → s/e is liver toxicity
* Selegiline / Rasagiline → Antioxidant property
* Ergot derivatives → s/e is
  - Vasoconstriction
  (Gangrene at site of end arteries)

* Amantidine → causes s/e livedo reticularis.

* Non ergot derivatives are DOC for Restless leg syndrome.
* Rotigotine → Skin patch
* Ropinirole, Pramipexole } Oral

Levodopa

* DOC for Parkinson's disease.
* Lipid soluble, given in inactive form

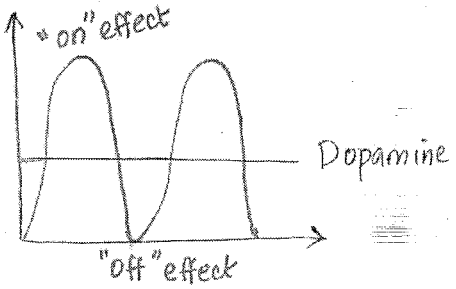
Levodopa (lipid soluble) (cross BBB) —Vit B6 / DOPA decarboxylase→ Dopamine (lipid insoluble)

* If levodopa to DA conversion happens in PNS → can't enter CNS → so give PNS inhibitor along with levodopa.
* PNS ⊖ → Carbi DOPA, Benserazide
  ↓
  ↑ availability of levodopa in CNS.

* PK:

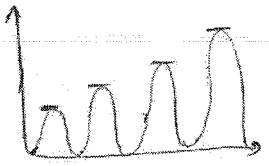
1) Oral route
(most efficient drug for Parkinson's disease)

2) $t_{1/2}$ <<< (on & off phenomenon)

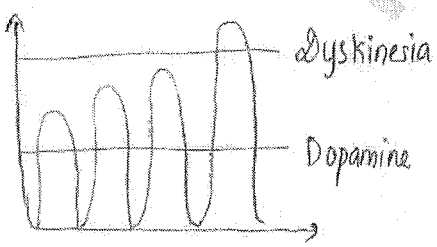


Since less $t_{1/2}$, effect fluctuate & k/a on & off phenomenon. So multiple times given daily.

3) Tolerance (↑ dose)



4) Dyskinesia (↑↑ dose)



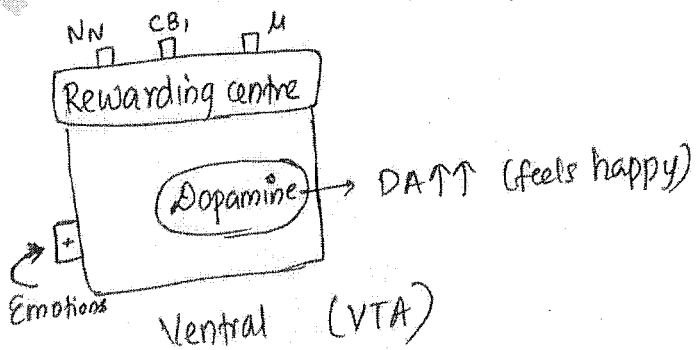
S/e of Levodopa

* ↑ levels in CNS → psycholic symptoms, hallucination, euphoria
* ↑ levels in PNS → ↑ β_1 → ↑HR, Arrhythmia, ↑ α_1 → HTN.

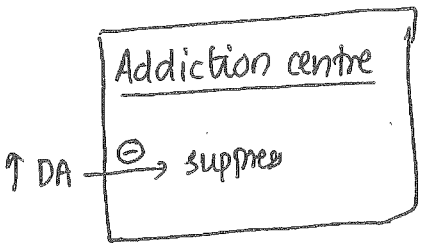
2) Alzheimer's disease:

* ↓ Ach (deficiency)
* Give AchE ⊗ (lipid soluble)
  ① - Donepezil (∞DOC)
  - Rivastigmine
  - Galantamine
* Also use Memantine (NMDA
  ② receptor ⊗) (N-methyl di aspartate)
* Dihydroergotoxin (ergot derivative)
  ③ - Cranial vasodilator (↑ blood supply to cranium)
  ↓
  thus removes free radicals from the cranium.
  ④
* Piracetam (Noo tropic agent)
  nerve growth

Drug Deaddiction.

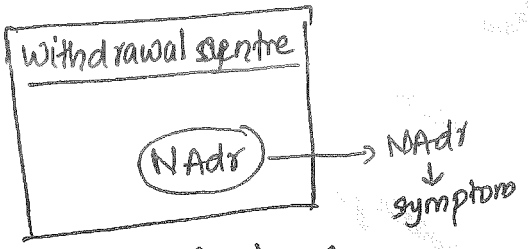


N_N → Smoke
CB_1 → Cannabis
μ → Opioids.



Nucleus Accumbens

* When ↓ DA → addiction centre activated → and ~~activates~~ ↑ dopamine k/a cravings.
* Relapse → Forced to take drug due to activation by addiction centre.
* When cravings are not satisfied by relapse → withdrawal centre activated



Locus Ceruleous

* Drug addicts come to clinic with withdrawal symptom.
* Withdrawal symptom is treated with analogue / agonist of drug.
  ↓
  Unstable patient become stable
* So to get rid of that completely → deaddiction / craving → Analogue / Agonist in high dose and then gradually reduce the dose. (6-8 months)
* High chance of relapse → so block ventral tegmental area with antagonist
* When ~~excess~~ toxicity → give antagonist.

Nicotine

* cigarettes, tobacco
* Nicotine receptor present in VTA is $\alpha_2\beta_2$ → ↑ Dopamine

1) Withdrawal
   - Give Nicotine (analogue) in the form of nasal spray.

2) Deaddiction / cravings
   - Nicotine as skin patch (DOC)
   - Varenicline (partial agonist of Nicotine N (N_N) receptor
   - Bupropion (Atypical antidepressant) Dopamine reuptake inhibitor
     ↓
     ↑ Dopamine.

3) Relapse:
   - Give antagonist Mecamylamine (N_N ⊗)

4) Toxicity:
   - Mecamylamine (i.v)

5) e-cigarettes (cylindre with smoke coming - resembles actual cigarette → psychological relief)

6) Consume sweets (↑↑ calorie diet)
↓
Used to reduce cravings..

Cannabis

* CB_1 ® ↑ → ↑ dopamine

1) Withdrawal ⇝ ↓ Deaddiction ↓ craving
(i.v) ↑ ∅ronabinol ↑ (oral)
(CB_1 ↑↑) Canalogue)

2) Relapse ↓ Toxicity
(oral) ↑ Rimonabant ↑ (i.v)
(CB_1 ↓↓) Cantagonist)

Ethanol

* MOA →

a) $GABA_A$ ↑↑ (agonist) → • Sedation ↓ Drowsiness
• ↓ Anxiety
• Loss of judgement

b) Acts on NMDA ® → Blocks it
• Temporary Amnesia

c) Unknown ® → Release of endorphin (natural ~~opoid~~ opioid)
↓
μ (VTA)
↓
↑ ∅opamine
(euphoria)

Opioids

1) Withdrawal ↓ Deaddiction ↓ craving
(iv) ↓ ↓ (oral)
+ μ → Methadone
± μ → Bupremorphine
(partial agonist)

2) Relapse ↓ Toxicity
↓ − μ (Cantagonist) ↓
Naltrexone
(slow onset)
∅OC
(oral)
Naloxone
(fast onset)
(i.v) > (intratracheal)

• PK

* Oral (ROA) (Abuse)
* Rx. of Methanol poisoning → iv
* ~~A~~ medicine is absorbed from upper GIT
* ↓ with NSAIDS → absorption will increase.
* Plasma concentration:
- < 0.003 gm/dl alcohol
↓
No problem to drive.
- > 0.083 gm/dl → loss of judgement

>0.3 → Coma

>0.4 → Death (↓RR, ↓VMC)
(GABA$_A$↑)

* Breath analyser (amount of alcohol in breath) (0.05%)

* Pregnant → consumes alcohol → baby will also become addict
↓
"Fetal alcohol syndrome"
- Microcephaly
- Flat & long philtrum (above upper lip b/w nose)
- Thin upper lip
- Epicanthal folds.
- Hyperactive
- ↓ Attension span
- Poor academic performance.

• Metabolism

* In liver → metabolized by dehydrogenase & CYP 450 enzyme

* Dehydrogenase:

Ethanol
↓ Alcohol dehydroge
Acetaldehyde
↓ Aldeh. dehydro
Acetic acid
(Kreb's cycle) ↓
$H_2O + CO_2 + ATP$

* Alcohol follows zero order kinetics

• Rx:

1) Withdrawal
- GABA$_A$↑↑ → DOC is Chlordiazepoxide.
- If with seizures & altered consciousness → k/a
Delirium tremors
↓
Rx: Lorazepam / Diazepam

2) Deaddition / Cravings:
(Alcohol acts on mulliple pathway → so difficult)

• GABA$_A$↑ → Chlordiazepoxide
+
NMDA (⊗) → Acamprosate
+
(??) Endorphin → Emotional support.
(Wife)

3) Relapse:
- Antagonist of μ (R) is best
- DOC → Naltrexone (μ ⊗)
- Disulfiram
Aldehyde dehydrog. (⊗)
(Non competitive)
↓
↑ Acetaldehyde accumulate
↓

↓

Nausea & Vomiting, Muscle Cramps, Insomnia, Tinnitus, Seizures.

- Toxicity:
  - * No antidote (multiple pathway of action)
  - * Provide supportive care: A B C
  - * Vit B_1 ↓↓ → Psychotic symptom → Give inj. Vit B_1 (thiamine)
  - * Aggressive → Inj. benzodiazepine (sedation)

CVS

HTN

* When BP > 140/90
* Antihypertensives are 4 types

1) Diuretics:
   - Loop diuretics (furosemide) (20% Na loss) → Rx. of HTN crisis (most efficient)
   - Thiazides (intermediate efficiency) → For maintenance Rx.

↓

Chlorthalidone, Indapamide, Hydrochlorthiazide → Acts on early DCT (Na^+ 10% loss)

2) ANS:

(i) α-blockers
- Direct vasodilation
- Prazosin (α_1 ⊗) (for HTN crisis)
  - DOC for HTN crisis caused for scorpion & black widow spider toxin
- Phentolamine ($\alpha_1+\alpha_2$ ⊗) (reversible)
  - DOC for cheese reaction & clonidine withdrawal syndrome.
- Phenoxybenzamine ($\alpha_1+\alpha_2$ ⊗) (irreversible)
  - DOC for pheochromocytoma.

(ii) β-blockers:
- Gen-II → β_1 ⊗ → ↓ CO → ↓ BP
  - BP = CO × PR
  - ↓ (SBP), ↓ (DBP)
  - (Systolic BP - SBP, diastolic BP)
- Gen III → β (×) → ↓ CO
  - Also has vasodilator property → ↓ PR → So used for HTN crisis

- Labetalol (DOC in PIH)
- Esmolol (HTN crisis)
- Nebivolol

(iii) Ganglion blockers :

- N_N ⊗ (sym ganglion ↓↓)
- Hexamethonium
- Trimethaphan

(HTN → Hexa-, Tri-, N_N)
↓
Rx of HTN crisis.

(iv) α_{2A} receptor agonists :

- CNS → ↓ VMC (Vasomotor centre) → ↓ BP
- Clonidine
- α-methyl dopa
- Used only for maintainence Rx.
- DOC for maintanence Rx of PIH.

3) Vasodilators :

* Site of action (SOA) → Blood vessels → Vasodilation → ↓ BP

(i) K^+ channel openers

- K^+ efflux → hyperpolarizatn (more -ve) → Vasodilation
- Minoxidil (given as prodrug)
- Hydralazine
- Diazoxide

- Minoxidil (prodrug) —liver→ M. sulfate (active form)
  - C/I in pregnancy
  - Given oral
  - Maintainence Rx of HTN
- Hydralazine & Diazoxide
  - Active form
  - Maint. Rx of HTN crisis
  - Safe to be used in pregnancy
  - s/e ⇒ 1) ↓ BP
    2) Reflex tachycardia
    (BP = CO × PR, ↓BP → ↓PR
    ∴ CO ↑ by signals from VMC → so reflex ↑ HR)
    3) ↑ blood supply to hair follicles
    (↑ proliferation)
    ↓
    Hypertrichosis
    (Hirsuitism)

⇒ Minoxidil → Rx of the androgenic alopecia in ♂

4) Open up K^+ channels on surface of β-cells → Hyperpolarizatn → ↓ insulin → ↑ glycemia

(∴ Diazoxide → Rx. of insulinoma)

(ii) Ca^{2+} channel blockers (CCB)

(L-type)

* Ca^{2+}_L ⊗ → Vasodilation

CCB

Old CCB

- Verapamil
- Diltiazem

* Less specific & less potent

Indications

1) Blood vessels → mild V.dilation → used for maint. Rx of HTN

2) Heart → Nodes ⊗ → ↓ HR → used for classical angina, Arrythmias → Supra ventricular arrythmia (SVT)

3) GIT → Relaxed → Rx. of GIT spasm. (Anal fissures) → (stool softners, muscle relaxant)

New CCB

- Ends with (-dipine)
- Also k/a Dihydropyridine

eg: Nifedipine

- More specific & more potent.

Indications

1) B. vessel → strong vasodilator →
   a) HTN → Maint. Rx / Crisis
   - Maint. Rx of HTN: Amlodipine
   - HTN crisis: - Nicardipine, - Clevidipine
   - DOC for maint. Rx in old & black patients: Amlodipine
   b) Vasospastic Angina/ Prinzmetal Angina.
   - Nifedipine
   - Amlodipine

New CCB (Indication)

c) Pulmonary HTN (Nifedipine, Amlody) (Idiopathic pulmonary)

d) Subarachnoid Hemorrhage

DOC → Nimodipine

(Hemorrhage → vasospasm in brain → Brain ischemia)

[Surface of vessels & Heart Ca^{2+} L type channel

On nerves → Ca^{2+} T-type]

e) DOC in peripheral vascular disease: Nifedipine.

2) Acts on gravid utenus (pregnant utenus)

Tocolytic (relaxes utenus) → DOC for preterm labour: Nifedipine.

S/e:

Old CCB

1) ↓ HR (Chronotropic)
2) ↓ CO (Ionotropic)
3) Heart block (Dromotropic)
4) Constipation: Verapamil > Diltiazem

⇒ Since ↓ CO → C/I in acute decompensated CHF.

s/e of new CCB

* ↓BP
* Reflex tachycardia
* Pedal edema (only arteries dilated not veins dilated)
* Gum hypertrophy (Nifedipine)

⇒ ♀ with heart disease already & preterm Labor → avoid Nifedipine (can cause reflex tachycardia)

↓

Here can use $MgSO_4$ / Atosiban

($MgSO_4 \rightarrow Mg^{2+}$ & Ca^{2+} cannot differentiate so no Ca^{2+} entry → no contraction)

↓

Oxytocin is also used here.

⇒ Best tocolytic is Nifedipine.

PK of CCB

* Lipid soluble (so cross BBB → acts on CNS → metabolized by liver - CYP3A4 enzyme
* $t_{1/2}$ >>> for Amlodipine

Vasodilator (continuation)

(iii) Nitric oxide donor (Vasodilat^n)

• Nitroglycerine

DOC for HTN crisis, Known case of Angina / MI

• Sodium Nitroprusside:

- DOC for intraoperative HTN crisis.
- When high dose used → cyanide toxicity

$CN^- + Hb \rightarrow$ CyanoHb (can't carry O_2)

↓

DOC in cyanide toxicity is Hydroxycobalamine (iv)

(CN^- → utilized → forms cyanocobalamine) → Vit B_{12}

↓

2nd regimen for cyanide toxicity

Na nitrite + Na thiosulfate

or Amyl nitrite

(iv) α_1 receptor agonist (vasodilat^n)

- Fenoldopam
- Rx. of HTN crisis.

(4) Renin Angiotensin Aldosterone system (RAAS)

* Angiotensinogen $\xrightarrow[\text{Liver}]{\text{Renin (RI)}}$ Angiotensin I $\xleftarrow[\text{(lungs}]{\text{(ACEI) ACE}}$ Ang-T II

AT-I ↓ $\xrightarrow[\ominus]{\text{ARB}}$ AT-II → AT_1 receptor → Action

* Angiotensin cause vasoconstriction, Na+ & H_2O retension, in remodelling of heart (CHF), glomerulosclerosis (fibrosis of glomeruli) (→ proteinuria)

Angiotensin causes
- Vasoconstriction
- Na^+-H_2O retension
- Remodelling of heart (CHF)
- Glomerulosclerosis (proteinuria)
- ↑ ADH release (CNS)
- ↑ thirst frequency

a) Renin Inhibitors
1) Renin synthesis inhibitor
Direct renin ⊗
2) Renin release ⊗
- α_2A agonist (clonidine)
- β ⊗ (Atenolol)

* Direct renin ⊗
Aliskiren
(Rx of HTN)

b) ACEI (ends with -pril)
- Captopril
- Enalapril
- Ramipril

Indication
1) HTN → Maint Rx → All
→ Crisis →
- Captopril
- Enalaprilat
↓
Used in HTN crisis associated with Scleroderma.

- DOC in young (<55 yr) & Non black.
↓
All ACEI

2) DOC for cardiac remodelling in compensatory CHF
3) DOC for Albuminuria (in diabetes mellitus)
4) Gout Rx (uric acid eliminate ↑↑ → uricosuric effect
5) ± DM retinopathy
(Diabetic Proliferative retinopathy → prevents proliferation of blood vessel in BV)

PK of ACEI
* All ACEI are prodrug except Captopril, Lisinopril.
* All ACEI → eliminated through kidney except fosinopril
Fosinopril < liver (50%) / kidney (50%)
* $t_{1/2}$ → >>> : Lisinopril
→ <<< : Captopril
* Enalapril (prodrug) —liver→ Enalaprilate (active) (stable compound)
↓
Used as a seperate drug for HTN crisis (iv)

* when consumed after food, their absorption is not reduced except captopril (↓ absorption)

S/e & C/I of ACEI

C - Cough
A - Angioedema } ACE needed for bradykinin metabolism → ACEI → ↑ BK → B_2 ® → ↑ PG → Edema

P - Pottasium ↑↑ (So C/I in K^+ sparing diuretics)

T - Taste change (Dysguisea) (due to electrolyte imbalance → affects sensory nerves)

O - Orthostatic ↓ BP (rare) [Captopril + Diuretics → Na^+ & H_2O loss ↓]

P - Pregnancy (C/I) (Baby born with kidney abnormalities → ↓ urine output → oligohydramnios)

R - (C/I) in Renal artery stenosis (bilateral) (↓ GFR is ACEI given)

I - Increase creatinine level (C/I when serum creatinine > 2.5)

L - Laal rashes (red) (Red skin rashes)

C) ARB (Angiotensin Receptor Blockers)

* AT, ⊗
* ARB ≈ ACEI
* No cough & angioedema as s/e
* Ends with (-sartan)
  - Losartan
  - Candesartan
  - Telmisartan

Treatment of HTN

Maintanence Rx:

1) < 55 yr, Non black
   ACEI > ARB

2) > 55 yr, Black
   CCB (-dipine)

* If no controll in BP after them
  ↓ (add)
  Use ACEI + CCB
  ↓ ~~(add)~~
  Again if no relief
  ↓ (add)
  Diuretics

HTN crisis Rx.

1) Diuretics
   - Thiazide
   - Furosemide ✓

2) ANS:
   - α ⊗ (PPP)
   - β ⊗ (Gen III – L, E) Labetalol, Etenolol
   - N_N ⊗ (HTN)
   - $\alpha_2 A$ ↑

3) Vasodilators:
   - D_1 agonist (F. Dopam)
   - CCB (Nicardipine)
   - K^+ ↑↑ (H, D)
   - NO ↑↑ (NTG, Na. Nitroprus)

(Nicardipine is DOC for HTN crisis if no unique indication is given)

4) RAS:
   - RI
   - ACE I (captopril, Enalapril)
   - ARB.

PIH

* Fetus safety is very important
* Teratogenic potential
  - Class A, B, C, D, X
  - Class A → safe without monitoring.
  - Class X: C/I to pregnant
  - Class D: Teratogenicity, so used when mother under life threatning condition
    Na. Nitroprusside.
  - Class B, C (Complete studies not available. So can be given to pregnant ♀ with monitoring)
  - Class B → Only α-methyl DOPA ↓ DOC for maintanence Rx
  - Class C → Labetalol (DOC crisis) Hydralazine Diazoxide Nifedipine Prazosin
  - Class D → Nitroprusside
  - Class-X → ACEI/ARB/ Diuretics

Pulmonary HTN

1) PGI_2 ↑↑ (Prostacyclin analogue)
   (↑ cGMP → Vasodilation)
   - Epoprostenal
   - Iloprost
   - Treprostril

- Most efficient

- DOC for idio refractory causes of pulm. HTN
- DOC for non idiopathic causes of PAH.

2) Endothelin ® ⊗

* Are ETA ⊗
* Bosentan, Ambrisetan

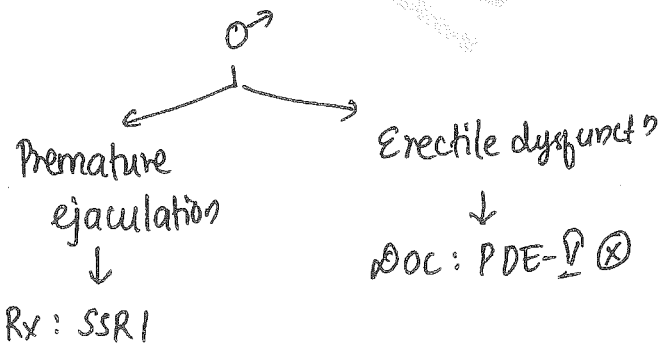
3) PDE-V ⊗

(↑cGMP → Vasodilation)

- Sildenafil
- Tadalafil

• V.dilatn in penis → Erection
DOC for erectile dysfunction

• S/e (Sildenafil particularly)
- Blue vision (retinopathy)



4) CCB: Nifedipine, Amlodipine

5) Nitroglycerine

ANGINA

1st line drug:

1) Nitrates
2) Ca^{2+} channel blockers
3) β-blockers

2nd line drug:

1) Ranolazine
2) Trimetazidine
3) Ivabradine
4) Nicorandil
5) Fasudil

2nd line drugs

1) Nitrates:

* MOA: NO↑ → ↑ guanyl cyclase → ↑cGMP → Vasodilation.

* Maximum action:
Systemic veins > Coronary arteries > systemic arteries.

Indication

1) DOC in Angina (1st drug)
• Coronary vasodilation → ↑ ↑ blood blow towards cardiac muscle → relieve in episode of angina.

- Acute episode of angina :
  Nitroglycerine (NTG)
  - Sublingual > i.V

2) Also given for Rx. of HTN crisis

- NTG → DOC associated with Angina / MI.

2) ↑↑ lipid soluble :
   sublingual → fast rate of absorption.

* BBB → CNS → Cerebral Vasodilation → stretching of meninges → Headache (s/e)

3) $t_{1/2}$ → long : ISMN
   — short : Amyl Nitrite

4) Liver metabolism.

s/e

1) MC → Hypotension (↓ BP) (Vasodil)
2) 2nd MC → Headache.
3) Skin flushing
4) Tolerance / Tachyphylaxis.
   ↓
   Monday's disease / syndrome.

Toxicity

* Hb (Fe^{2+}) $\xrightarrow[\text{(Nitrate)}]{\text{high dose}}$ Meth Hb (Fe^{3+}) → O2 carry capacity ↓↓↓

Rx : Methylene blue
(Fe^{3+} → to Fe^{2+})
(Methhemoglobinemia)

C/I

1) ↓ BP (SBP < 100 mmHg)

2) PDE-V ⊗ → V. dilation
↳ (↑ cGMP) ↗

2) β-blockers:

* Generation II β ⊗ → ↓ HR
→ Classical Angina Rx.

3) CCB:

* Old → ↓ HR, Classical Angina
* New → Vasodilat^{n}, Vasospastic Angina.

Second line drugs for Angina

1) Nicorandil

* Opens K^+ channel → Coronary vasodilation.

2) Ivabradine

* funny current (I_F) inhibitor
* Leaky current inhibitor
* Na^+ K^+ exchange current ⊗

↓

Responsible for automaticity of SA node. So it ⊗

↓

↓ HR

↓

↓ O_2 demand.

* s/e: Vision defects.

3) Ranolazine:

* Blocker of late Na^+ current
* PFOX ⊗ (partial fatty acid oxidation inhibitor)

4) Trimetazidine:

* PFOX inhibitor

5) Fasudil:

* Rho kinase inhibiter (type of protein kinase)
* Causes vasodilation.

ARRYTHMIA

* Classification of Anti-arrythmic is known as Vanghan William classification

1) Class-I → Na^+ channel blocker
→ Rx. Ventricular Arrythmia.

i) Class Ia: Na^+ channel ⊗ & K^+ channel ⊗

ii) Class Ib: Na^+ ⊗, open K^+

iii) Class Ic: Na^+ ⊗

* Ia → • Procainamide
- Rx Ventri. arrythmia
- Rx. Atrial flutter
- Rx. of WPW syndrom (Wolf Parkinson White)

PK: Liver (Acetylation

s/e : SLE like reaction.

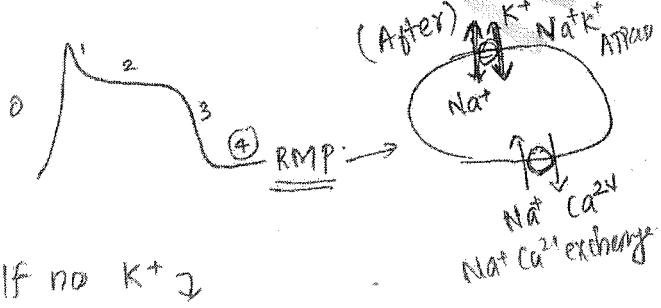
- Quinidine ≈ Quinine
  - from Cinchona tree
  - s/e: N_N ⊗ → ↓BP
    Hypoglycemia.
  - Toxicity : k/a Cinchonism
    (Tinnitus, Seizures, Death)

(So outdated nowadays)

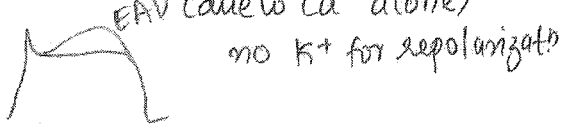
- Disopyramide :
  - Anti cholinergic s/e

⇒ Common s/e of Procainamide, Quinine & Disopyramide.

- QT prolongation
- Torsade de pointes.
- Widening of QRS complex
- EAD (early after depolarizat°)



If no K^+ ↓



If ↑↑EAD

QRS complex → k/a polymorphic Ventricular Tachycardia Torsade de pointes

⇒ β_1^{sym} → stimulates funny channels → produce funny current → leads to phase 4 in nodal AP.

* Class Ib

i) Lidocaine
ii) Mexiletine
iii) Phenytoin
iv) Tocainide.

- Lidocaine → high first pass metabolism → so given i.v
- Also lidocaine is DOC for Ventricular fibrillation
- s/e of lidocaine toxicity:
  - CNS toxicity
  - Agitation.
  - Tremors.
- Mexiletine → same like lidocaine but given orally.
- Phenytoin → used as antiepileptic (used for ventricular type of arrythmia)

* Class Ic

- Moricizine
- Propafenone
- Encainide
- Flecainide

- Highly efficient
- Used for refractory type of Ventricular Arrythmia.

2) Class II ⟹ β (x)

* β_1 ⊗ → ↓HR < Nodes – SVA / Muscles – VA

SVA : Supraventricular Arrythmia (nodes above ventricle)

VA : Ventricular Arrythmia.

* Esmolol (max. Antiarrythmic)
  Metoprolol
  Propranolol

* DOC for arrythmia with myocardial infarction.

* β (x) acts on phase 4 of AP (leaky current needs β_1)

* So β ⊗ blocks DAD in phase IV (↑ DAD in MI)

DAD – Delayed after depolarizⁿ

3) Class III → Blocks K^+ channels.

* S/e : QT prolongation
  EAD ↑↑
  Torsades de pointes

(So Class I_a & class III have this 3 s/e)

(i) * Amiodarone

↓

Amiodarone

* Broad spectrum antiarrythmic
* I → Na^+ ⊗, II → β ⊗,
  III → K^+ ⊗, IV → Ca^{2+} ⊗
* Used in SVA & VA
* DOC for heart block with arrythmia.
* PK → long $t_{1/2}$ (2–3 months)
  → Strongly bound to plasma proteins.
  → ↑↑ lipid soluble (so can enter all tissue)
  → Metabolized by liver → CYP450, P-glycoprotein pump.
  → If this enzyme pump ⊗ → can't metabolize and drug interactions are common.
* S/e : (of Amiodarone)
  (I_2 → I^+ free radical)

↓

Pls – Peripheral neuropathy, phototoxic (↑ pigmentation → if blue – Blue man syndrome)

Check – Corneal deposit
PFT – Pulmonary fibrosis (dry cough)
LFT – Liver fibrosis (granulomatous)
TFT – ↑ T_3 (Acute)
T_4 ⇌ T_3 ↓↓ (chronic)

ii) Sotalol

* β ⊗ << K+ ⊗
Class II Class III

* In supraventricular arrythmia (SVA) and ventricular arrythmia.

iii) IButilide } (Highly effective)
iv) Dofetilide } Refractory A fibrillation

Class IV

* Ca^{2+} (L-type) ⊗
* Nodes → SVA
* Verapamil, Diltiazem.

Class V (Miscallaneous)

i) $MgSO_4$ (i.v)
* Blocks Ca^{2+} entry in cardiac muscles
* Ventricular Arrythmia
DOC in Torsades de pointes

ii) Digoxin (Vagomimetic)
* ↓ HR (AVnode > SA node)
* Used in Supraventricular arrythmia (SVA)

(iii) Adenosine:
* K^+ channel opener in AV node > SAN
* Hyperpolarization → Rx SVA
* DOC in PSVT (Paroxysmal supra ventricular tachycardia)
* Pk
→ Given iv
→ Loading dose : 12 mg
→ t½ → 10sec
→ RBC metabolism (converts it to 5' AMP)
* s/e ⇒ Causes bronchoconstriction (so precipitates bronchial asthma)

CHF

CHF (↑ congestion ⊗ pump)

Acute decompensated heart failure
↓
(unstable)
• EF < 40%
• Cardiogenic shock
↓
1) ↓ congestion by giving Furosemide (i.v) (Diuretics) or Nesiritide (Natriuretic peptide analogue)
2) ↑ pumping by Inotropic drugs
– Best: Dobutamine
(continues →)

Compensated heart failure
↓
(stable)
• EF > 40–60%
(Oral route)
↓
Rx : $
(i) Remodelling ↓
ACEI > ARB
β ⊗ / Ald. ⊗
Best → ACEI ⊕
(continues) ↳

⇒ Dobutamine will not be used in the following

Acute decompensated CHF (continuation)

(a) CHF with oliguria
Dopamine (2-10)

(b) CHF with ↓ systolic BP < 70 mmHg
NAdr > Dopamine.

(c) CHF with pulmonary HTN
(Inodilators)

- MOA → PDE III ⊗

↑ cAMP → ↑↑ contraction of muscle → ↑ CO

↑ cGMP → Dilate pulmonary artery → ↓↓ PAH (Pulm. artery hypertension)

- Amrinone, Milrinone

S/e: Bonemarrow ↓ (Thrombocytopenia)

(d) CHF ± Arrythmia:
Digoxin

- ↑ CO → ↑ inotropic → Na^+K^+ ATPase ⊗

- ↓ Chronotropic / ↓ dromotropic → ↓ Nodes (Vagomimetics), ↓ HR, ↓ Arrythmia.

- Usually drugs either ↑ or ↓ all 3 effects → Inotropic, Chronotropic, Dromotropic
But digoxin ↑ iono, ↓ chrono & dromo.

PK:

- All inotropic drugs (i.v)
Digoxin → Oral, i.v

- All inotropic drugs $t_{1/2}$ <<
Digoxin → 40 hrs.

S/e

* All cause ↑ HR, Arrythmia except Digoxin (↓ HR)

3) ↓ Pulmonary Edema:

- Venodilation → ↓ EDV → ↓ pulmonary blood flow → ↓ pulmonary edema.

- DOC: Furosemide > Morphine > Nitroglycerine (NTG)

Compensated HF

(2) Rx. congestion (↓ it)
- Furosemide (oral)

(3) Prevent ↑ HR ⊕
- β ⊗ / Ivabradine. (funny current ⊗)

⊕

4) Vasodilator
- ↑ afterload
- ACEI / _dipine / Hydralazine

- Tab ACEI
- Tab Furosemide
- Tab β(x)
- Tab Nifedipine

Compensated HF.

- i.v furosemide
- i.v Dobutamine
- i.v Morphine

Decompensated HF

⇒ Severe HF. (after long term compen or decomp. HF leads to this)
- Inotropic support.
- Maintainence therapy
- Oral - Digoxin.

Cardiac glycosides

Digitalis (from plant → Foxglove)

- Digoxin (metabolized by kidney)
- Digitoxin. (Outdated) (metabolized by liver)

MOA

* Non specific

1) Muscles → Na^+K^+ ATPase (x) (Non competitive)
↓
↑ Ca^{2+} in cytoplasm
↓
↑ Inotropic → ↑CO

2) Lipid soluble → cross BBB
→ acts on medulla → stimulates medulla → ↑ vagus → Inhibits AV node & SAN → ↓ HR & ↓ conduct^n velocity → ↓ O_2 demand

Indications of Digoxin

1) CHF
- Acute decompensated CHF
CHF ∈ Arrythmia (iv)
- Maintanence Rx in severe CHF (oral)

2) Anti Arrythmic (by acting on nodes)
so Rx. SVA (supraventricular arrythmia)

PK

* Oral / iv
* Absorption → good in oral.
* In plasma, narrow therapeutic index → so need therapeutic drug monitoring (0.2-2 ng/ml)
* Eliminated by kidney > Liver (exception)
* In kidney eliminated by p-glycoprotein pump.
* Lipid soluble → reach CNS
* $t_{1/2}$ - 40 hrs

s/e of Digoxin:

1) Nausea & Vomiting (MC s/e) } s/e of non specific drugs
2) Hypersensitivity reaction }
3) Arrythmia → ↑ Ca^{2+} overload in muscle → automatic contraction → Ventricular arrythmia (MC: Ventricular Bigemming)
4) Rare s/e ⇒
   - Yellow vision
   - Gynaecomastia
   - Delirium
   - Neuralgia.

Toxicity of Digoxin

* Arrythmia → Death
* PSVT with Heart block.
  (PSVT - Paroxysmal supra ventricular tacchycardia).
  ↓
  - Atria > 250 b/min
  - AV block
  - Ventricle < 40 b/min

* DOC for digoxin toxicity
  Digibind (i.v)
  (Ab to Digoxin structure)

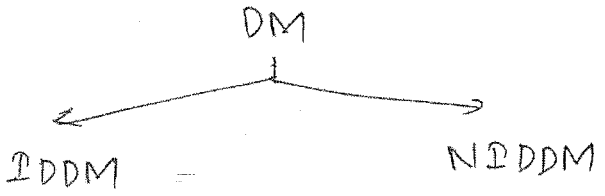
* Factors precipitating toxicity
  1) ↑ Ca^{2+} → ↑ Ca^{2+} entry to muscle → ↑ Arrythmia
  2) ↓ Mg^{2+} → ↑ Ca^{2+} entry through Mg^{2+} channel → ↑ Arrythmia.
  c) ↓ K^+ (Digoxin binding to ATPase is more)
  d) Patient suffering from kidney failure → ↓ elimination
  e) Old age → compromised kidney function
  f) If taking P-glycoprotein inhibitor drugs like:
     - Quinidine
     - Amiodarone
     - Verapamil
     - Diltiazem
     - Erythromycin
     - Ketokonazole
     - Itraconazole.
  g) ↓ K^+ by furosemide, thiazides.
  h) Thyrotoxicosis → ↑ HR → Arrythmia.

C/I of Digoxin:

1) All ionotropic C/I for HOCM (Hypertropic Obstructive Cardiomegully)
   DOC → β ⊗
2) WPW Syndrome (Wolf Parkinson White syndrome)
   (If digoxin is given then precipitates arrythmia)

ENDOCRINE

Diabetes Mellitus

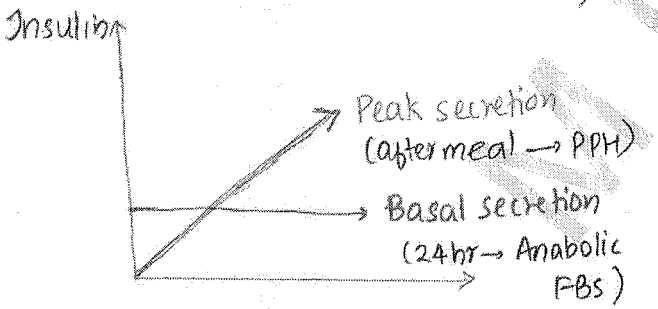


* Blood sugar:

	N	DM
Fasting →	< 110	> 126
Post prandial →	< 140	> 200

↓

Glucose intolerance (in b/w values)



* Insulin secretion → 2 types
  1) Peak secretion
  2) Basal secretion

PPH – Post Prandial Hyperglycemia
FBS – Fasting Blood sugar.

1) Insulin

* Humanised DNA insulin is used nowadays (less s/e)

a) Rapid acting
- Onset : 15 min (inj. just before meal)
- Drugs
  - Glulisine
  - Aspart
  - Lispro
  - Afrezza – Inhalation

} sub cutaneous (s.c)

b) Short acting:
- Onset : 30 min to 60 min

(i) Regular insulin (iv & sc)
(ii) Zn amorphous (s.c) (Semilante)
- If regular insulin in i.v ↓ DOC for Diabetic Keto Acidosis.

c) Intermediate acting
- Action : 14–16 hrs
- NPH (Isophane)
- Lente (30% Zn amorphous + 70% Zn crystalline)

d) Long acting
- Action : 20–24 hrs
- Insulin Glargine (Peak less)
- Insulin Determir

- Degludec (Long acting)
- Insulin Ultralante (Zn crystalline)

* All have slow onset, given for anabolic effect.
* Since slow onset, not used for PPH

Indications of Insulin

* DOC for DM-I
* DOC for DM in pregnant.
* DOC for Diabetic Ketoacidosis (Regular Insulin, i.v)
* DOC for DM-II with infection
  (MC infection in DM patient is UTI (urinary tract infection) Because frequent urination → good culture media for bacteria)

ROA

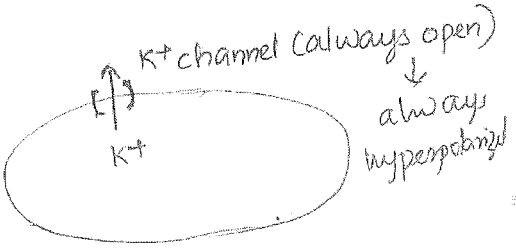
* Peptide → Oral ⊗
  sc > i.v > inhalational
* MC site of sc
  - MC Ant. abdominal wall leaving periumbilical area.
  - 2nd → Arms (b/w deltoid and elbow joint)

s/e of Insulin

* MC s/e is Hypoglycemia
* Weight gain
* Hypokalemia (So used in Rx of acute hyperkalemia)
* Pedal edema

2) Insulin secretogogues

* Site of action → β-cells of pancreas → ↑ insulin secretion.



β-cell

* Vagus → ACh → M_3 receptor
* Food → Glucose → ATP →
  ATP is inhibitor of K+ channel
  → so from hyperpolarization it comes to RMP state → M_3
  ↑ cAMP → opens Ca^{2+} channel
  → Ca^{2+} influx causes insulin release.
* K+ channel blockers
  - Sulphonyl urea
  - Meglinitides
* ↑ cAMP
  - GLP-1 analogues
  - DPP-4 ⊗ inhibitors.
* The above medicines are k/a insulin secretogogues

Sulfonylureas

* MOA : K^+ ⊗
* 2 types
  - Generation I (outdated)
  - Gen II (used)
* Gen-I :
  - Chlorpropamide
    (long $t_{1/2}$ → so ↑ in hypoglycemia)
  - Tolbutamide
    (zero order kinetics)
* Gen-II :
  (starts with Gl–)
  1) Glipizide (long $t_{1/2}$)
  2) Gliclazide
  3) Glyburide (safe in pregnancy)
  4) Glimepride
* S/E :
  i) Hypoglycemia
  ii) Weight gain
  iii) Pedal edema
  iv) Hypersensitivity reaction

Meglinides

- Repaglinide
- Nateglimide.

* Same as sulphonylurea.
* But they are less efficient
  → so hypoglycemia is less common.
* Also $t_{1/2}$ << → so given TDS (3 times)
  (thus poor compliance)

GLP-1 analogues

* Glucagon like peptide-1 / Incretin.
* ↑ cAMP causes
  (i) β-cell → ↑ insulin release
  (ii) α-cell → ↓ glucagon release
  (iii) Blood vessel → vasodilation → ↓ blood supply → ↑ proliferation of β-cells.
  (iv) cAMP ↑ in GIT muscle → relaxes → ↓ gastric motility → ↑ food storage → amount of food reaching small intestine is reduced at a given time → ↓ PPH (post prandial hyperglycemia)
  ↑ food storage causes ↓ food intake too.

V) ↓ Hb1AC (Glycosylated Hb)

* Drugs are
  - Exenatide
  - Liraglutide.

* Indication:
  → DM-II.
  → Obesity.

* S/e:
  1) Nausea & Vomiting (MC s/e)
  2) Weight loss
  3) Hypoglycemia
  4) Rare → Hemorrhagic Pancreatitis, Medullary Ca thyroid.

DPP-4 inhibitor

* Dipeptidyl peptidase.
* Blocks (S) action of GLP-1 that is metabolised by DPP-4.
  - Sitagliptin
  - Saxagliptin
  - Linagliptin
  - Vildagliptin.

* 5 actions → ↑ insulin release, ↓ glucagon release, ↑ β-cell proliferation, ↓ food intake, ↓ PPH, ↓ Hb1AC.

3) ↑ Glucose uptake in periphery

(i) Biguanides:
  - Metformin

* MOA
  - Skeletal muscle → ↑ glucose uptake.
  - Small intestine → blocks glucose absorption
  - MC mechanism in Liver → ⊗ glycogenolysis & ⊗ gluconeogenesis
  - Never shows hypoglycemia

* Indication
  1) DOC in DM-II
  2) DOC in glucose intolerance
  3) DOC for obesity associated with DM (weight-loss)
  4) DOC for PCOD.
     Metformin > OCP.

* S/e
  - MC is weight loss
  - Vit B_{12} ↓↓ → Megaloblastic anemia
  - Rare → Lactic acidosis (Metabolic acidosis)

ii) Thiozolidinedione

- Pioglitazone

*MOA - ↑↑ PPaR-γ →
↑ expression of GLUT-4 protein in skeletal muscle.
→ ↑ uptake of glucose → level of glucose ↓ in blood.

* s/e
- Weight gain
- Edema (severe) → leads to CHF
↓
Along with glu, Na^+ uptake
→ Na^+ ↑ → ↑ H_2O uptake
- ↑ risk of # (osteoporosis)
- ↑ risk of Bladder Ca (so outdated)

4) ↑ glucose elimination:

a) α-glucosidase inhibitor

* SOA → Small intestine mucosa.

* Only monosaccharides are absorbed. (so polysacch. breaks down to monosach)

* eg: Acarbose, Miglitol, Voglibose. } (blocks polysaccharide to mono. conversion)

* s/e : Flatulence (↑ gas)

* C/I in inflammatory bowel disease.

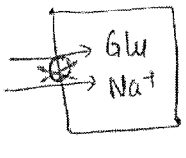
b) SGLT-2 ~~anta~~ blocker

* SOA → PCT in kidney

* SGLT-2 : Sodium glucose transporter-2.

* Drugs:
- Canagliflozin
- Dapagliflozin
- Remogliflozin
- Empagliflozin

* Leads to loss of glucose along with Na^+.



* s/e:
1) Weight loss
2) ↑ UTI
3) ↓ Na^+
4) ↓ BP

5) Miscallaneous

(i) Pramlintide

* Amylin analogue
* Inhibits glucagon release
* ↓↓ gastric motility
* ↓ PPH
* ↓ food intake
* For both DM-I & DM-II

⇒ Insulin & Pramlintide are used for both DM-I & II.

GONADAL HORMONES

Male gonadal hormones:

Hypothalamus
↓
GnRH
↓
(+) → (R) ← (−)
Pituitary
↓
LH & FSH
↓
Testes
↓ 17 α-hydroxylase (−)
Testosterone
↓ 5 α-reductase (−)
Dihydrotestosterone
↓
ARB (−) → Acts on Androgen receptor
↓

Actions of Testosterone:

- ↑ sperm
- 2° sexual characteristic ↑
- Bone/muscle mass ↑
- Bone length ↓ (premature closure of ~~testosterone~~ epiphysis)
- Scalp hairs ↓, other body hairs ↑
- Acne & folliculatis ↑
- Lipid profile ↓↓ (LDL ↑)
- Confidence ↑↑
- Aggression ↑↑
- Prostate ↑↑

* Androgen Receptor Blocker (ARB)
  - Bicalutamide
  - Flutamide
  - Nilutamide
  - ~~Nilutor~~ (All lutamide)
  - cyproterone acetate.

* 5-α reductase inhibitor (-ride)
  - Dutasteride
  - Finasteride

* 17α-hydroxylase inhibitor
  Abiraterone acetate.

* GnRH-Receptor antagonist (-relix)
  - Cetrorelix
  - Ganarelix
  - Abarelix

* GnRH-receptor agonist. (-relin)
  - Nafarelin
  - Guserelin
  - Buserelin
  - Leuprolide.

Androgen Receptor Blockers

* Used for Rx. of prostate Ca
  (– lutamide drugs)
* Cyproterone acetate : In Rx of
  - Prostate Ca
  - Acne & folliculitis in ♀
  - Alopecia in ♂
  - Hirsutism in ♀

5 α-reductase inhibitor

* Rx. of
  - BPH
  - Prostate Ca
  - Alopecia
  - Hirsuitism.

17 α-hydroxylase x (Abiraterone acetate)

* Only for Rx of prostate Ca

S/e of all ~~above~~ & (common)

1) ↓ sperm count
2) ↓ Bone & muscle mass
3) ↓ confidence
4) ↓ aggression
5) ↓ 2° sexual characteristics

⇒ GnRH – ® agonist & antagonist

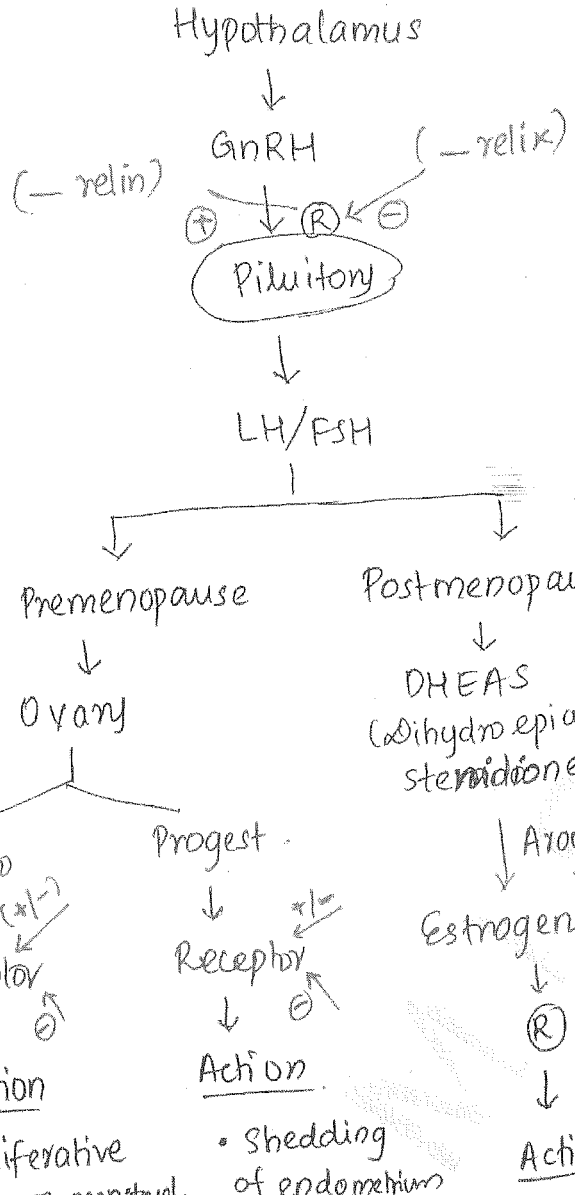
* Can be given to both male & ♀ (same pathway)

Agonist:
* If given pulsatile → ↑↑ homone
* If continous (as depot) → ↓↓ (due to down regulation)

* Prostate cancer (Rx)
  GnRH ↑↑ >> ↓↓
* Rx. of endometrical Ca, Breast Ca, Endometriosis, Fibroids, precocious puberty (DOC)
* In Rx. of hypogonadism (GnRH-R ↑↑ → pulsatile)
* In IVF (invitro fertilisation)

* S/e
  - ♂ same as before
  - In ♀
    - ↓ ovulation
    - 2° sexual ↓
    - Osteoporosis
    - Atrophy of breast & vulva
    - Dryness of skin and vagina.
    - Vasomotor symptoms of menopause.

Female gonadal hormones



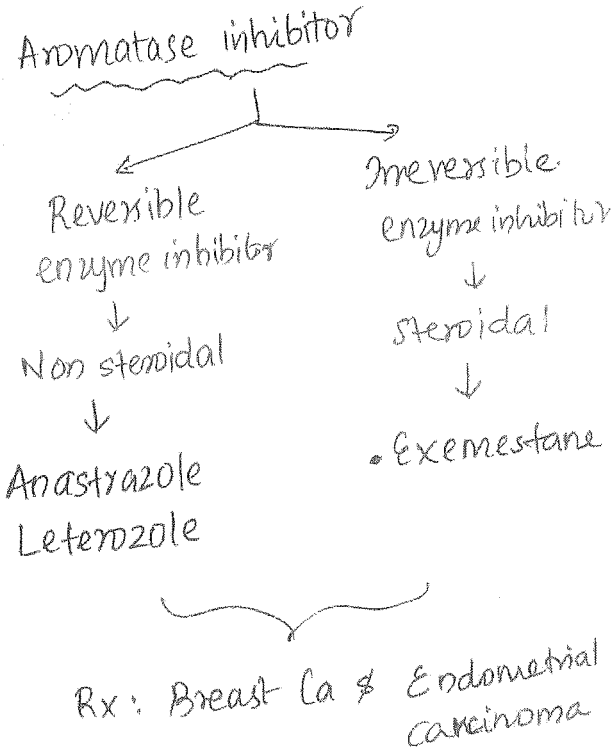
* Aromatase inhibitor:

* Estrogen ® +/– → selective estrogen receptor modulator (SERM)

* Estr ® (–) → SERD (selective estro. ® downregulator).

* Progesterone ® +/– → SPRM

* Prog. ® – → Mifepristone RU 486.



Thyroid Disorders

① Hormone Synthesis Inhibitor

* MOA → ⊗ Thyroid peroxidase → ↓ thyroid H synthesis

Thionamides

Carbimazole

- MOA: ⊗ Peroxidase
- PK: 1) $t_{1/2}$ >>> (once daily) Compliance: Good
2) Given as prodrug → liver → Active metabolite - Methimazole
3) Oral route, Slow onset of action → DOC for maintainence treatment of hyperthyroidism.
- s/e: MC is Acne & folliculitis
- Suppress bone marrow (Aplastic Anemia)

Propylthiouracil (PTU)

- MOA: ⊗ Peroxidase, ⊗ Peripheral conversion ($T_4 \rightarrow T_3$)
- PK: $t_{1/2}$ <<< (TDS) (3)
2) Given in active form
3) Oral or i.v, Fast onset of action → DOC for thyrotoxicosis
- s/e:
- MC → Acne & Folliculitis
- Liver toxicity (Fulminant Hepatitis)

Carbimazole

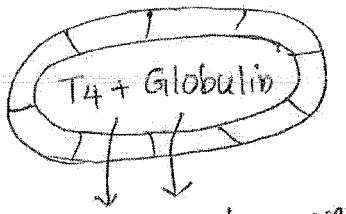
- s/e:
- Teratogenicity (Fetal Aplasia cutis) → Absent skin
MC site: Scalp

PTU

- s/e
- Less teratogenic
- Safe in pregnancy
- DOC for ↑T3 in pregnancy

② Hormone release inhibitors

* Site of action: Thyroid follicles
* MOA: ⊗ Proteolysis → Hormone release ↓↓↓



T_4 is Released whenever needed by proteolysis of T_4 + globulin complex

* Iodides:
- NaI
- KI
- Lugol's iodine (most efficient)

* s/e:
① - Highly teratogenic (C/I in pregnancy)

2)- Mucositis (inflammation of mucosa)
- Buccal mucositis
- Rhinorrhea
- Swollen salivary gland (↑ salivation)

3) - Hypersensitivity reactions (Interstitial nephritis)

4) - Lymphadenopathy

5) - Phototoxic reaction (↑ pigmentation of skin)

Indication

1) Used in thyrotoxicosis
- Fast onset of action
- ↓ release of thyroid
- Also K/a Thyroid constipating agents.

2) Wet cough (Expectorant)

3) Antiseptics (local route)
eg: Povidone iodine

4) Sporotrichosis (Antifungal)

③ Peripheral conversion inhibitors

* ⓧ $T_4 \longrightarrow T_3$ in plasma

* • PTU
• Prednisolone
• Propanolol

* Used in Rx. of thyrotoxicosis
* Fast onset of action.

Hypothyroid drugs

* T_4 (Levothyroxine)
It is a DOC in
→ Goitre
→ Hashimoto's thyroiditis
→ Cretinism

* Oral route, before meal
* After meal ⟶ ↓ absorption.

Radio-iodine

* Normal I_2 is I^{123}
* Radio I_2 is I^{131}
* Used in therapy
* I^{131} → Oral route → a liquid
* I^{131} → to thyroid follicles → emitts β-rays → starts destruction of thyroid glands from inside to out.
* In 90 days → complete destruction of thyroid gland
* Dose is calculated in μ curie
* $t_{1/2}$: 7-8 days (1 wk)
* Action : 28 days (4 wks) (after 4 $t_{1/2}$ drug completely eliminated)

* Rx :
  1) Cancer
  2) Metastasis (Thyroid)
  3) Grave's disease
  4) Hot nodule (active foci in gland which releases excess hormone in thyroid)

Bone disorders

Hormonal drugs

a) Vit D

* Source : (Sunlight) Skin / food
  Vit D_3 (Cholecalciferol) (inactive)
  ↓ Liver
  25 (OH) Vit D_3 (Calcifidiol) (partial)
  ↓ Kidney
  1,25 $(OH)_2$ Vit D_3 (Calcitriol) (active)

* Drugs → Cholecalciferol
  Calcifidiol
  Calcitriol

* Used in Rx. of
  - ↓ Vit D deficieney (Rickets, Osteomalacia)
  - ↓ Ca^{2+}

* Calcipotriol
  - Local application
  - Immuno modulant
  - Rx. of psoriasis

b) PTH

* Parathyroid hormone
* Peptide hormone → 84 aa
  1 - 34 aa : Active
* Teriparatide (-tide → peptide drug → cant given oral → given iv / s.c)
* Given subcutaneous (s.c)
* Rx :
  1) ↓ Ca^{2+}
  2) Osteoporosis
* PTH (released as pulsatile)
  ↳ helps in bone formation
* But PTH ↑↑ (continous manner) ↑↑
  ↳ ↑ bone resorption

c) Calcitonin

* Ca^{2+} ↑↑ entry in bone
  ↑↑ elimination from kidney
* Calcitonin ↓ serum Ca^{2+} level

* Used in Rx
  1) ↑ Ca^{2+}
  2) Osteoporosis
  3) Paget's disease

* Commercial : Salmon fish (present in it)
  - Given as nasal spray, subcutaneous, i.m

d) Estrogen

* Estradiol (E_2) → most active
  +
  Low dose progesterone.
  (HRT)
  ↓
  Reabsorption ↑
  ↓
  ↑ osteoblast → ↑ bone formation.

Non-hormonal drugs

1) Bisphosphonates :

* MOA : ↑↑ apoptosis of osteoclast
  ↓
  Osteoclast activity ↓
  ↓
  ↑ bone formation

* Rx. of
  1) DOC : Osteoporosis
     A → Alendronate
     I → Ibandronate
     R → Risedronate
     Z → Zolendronate
  2) ↑ Ca^{2+}
     Osteoblast Activity ↑ →
     so ↑ uptake of Ca^{2+} from plasma
  3) Osteolytic lesions of malignancy (Rx)
  4) Paget's disease.
     (for osteolytic lesions of Paget's disease)

* PK → Oral / i.v / i.m
  → Eliminated by kidney
  → $t_{1/2}$ → >>> : Zolendronate (1 yr)
  ↘ <<< : Alendronate (1 wk)

* S/e :
  1) Oesophagitis
     - MC local s/e
     - So to prevent it by
       i) taking with plenty of water
       ii) Empty stomach
       iii) Upright posture for 30-45 min
       iv) i.v / i.m route.
  2) ↑ acid production (GERD / PUD)
  3) Flu like symptoms
  4) Rarely → Osteonecrosis of jaw & femur head

2) SERM

* Selective Estrogen Receptor Modulator
* Tamoxifen, Ramoxifen (R > T)
* Oral
* Estrogen (R) ↑↑ → bone form^{n}
* Rx : Osteoporosis

3) Cinacalcet

* Its structure resembles Ca^{2+}.
* It gives negative feedback to parathyroid gland → ↓ PTH secretion.
* Rx : ↑↑ PTH

4) NaF

* Forms fluroappatite crystals
* It resembles hydroxyapatite crystals of bone → ↑ strength of bones & teeth.
* Rx : Osteoporosis

5) Miscellaneous drugs:

→ Strontium Ranelate
→ Denosumab (⊗ RANK ligand)
→ Both in Rx. osteoporosis.

Steroids

Mineralo-corticoids (Aldosterol) | Glucocorticoid (Cortisone) | Sex steroid (DHEAS)

---

* Aldosterone → ↑ Na^{+} & H_2O retension → ↑ BP
* Fludrocortisone : DOC in chronic ↓ BP
* Oral

⇒ Cortisone → ~~causes~~
- Anti inflammatory
- Anti allergic
- Immuno suppresant

⇒ Hydrocortisone, Betamethasone
Prednisolone, Triamcinolone
Dexamethasone
Methyl prednisolone

- DHEAs → ↑ Sexuality
  ↑ Anabolic
- Anabolic steroids
  - Nandrolone
- Used in ↑ body mass by body builders.

* Hydrocortisone activity is more close to natural form
  ↓
  So DOC for acute steroid deficiency (i.v)
  - Anaphylatic shock
  - Acute adrenal crisis (Waterhouse syndrome)
  - DOC for congenital adrenal hyperplasia (given to child after birth)

* Triamcinolone
  - Has max. topical activity
  - Rx: Fibrosis (local inj.)

* Dexamethasone, Betamethasone
  - Most efficient drug
  - Betamethasone > Dexamet.
  - Pregnancy → < 34 wk. delivery → given to ♀ for lung maturity
  - Used to suppress HPA axis for Rx. of
    - Cushings syndrome
    - Congenital adrenal hyperplasia (to mother)

s/e of Steroids
(In Bronchial Asthma)
(same)

Ant Pituitary

a) Antipituitary

* Growth hormone ↑ → Acromegaly
  Pegvisomant (GH ® ⊗)

* Prolactinoma → ↑ prolactin
  DOC: D2↑↑
  Cabergoline

* Pregnant ♀: Bromocriptine

Post. Pituitary

ADH (Kidney → done other)

Oxytocin

* Rx. of
  - DOC in PPH
  - Milk ejection
  - Induce labor

* Atosiban → Oxytocin R ⊗
  Pre. term labor
  ↓
  DOC: Nifedipine.

Hypothalamus

1) GnRH
2) Somatostatin
   - * ↓ GH release
   - * ↓ ACTH
   - GIT peptides:
     - * ↓ VIP
     - * ↓ Glucagon
     - * ↓ Insulin release
     - * ↓ Cholecystokinin
     - * ↓ Gastrin
     - * ↓ Enterochromaffin cells (5HT)

Drugs
- Octreotide
- Lanreotide

* Both are polypeptide
* Given s.c / i.v
* Used in Rx.
  - Acromegaly
  - Cushings
  - DOC for VIPoma
  - DOC for gluagonoma
  - DOC for insulinoma
  - DOC for cholecystokinin tumor
  - Rx: gastrinoma
  - DOC in Enterochromaffin cell tumor.

* GIT peptides → Vasodilation
  - ↑ secretion in GIT → ↓ secretory diarrhea (DOC)
  - Esophageal varices (DOC)

ANTI CANCER DRUGS
(7 types)

1) Alkylating agents

* MOA: Donate alkyl group ↓ Binds to N7 (of) guanine base present in DNA of cancer cells ↓ ⊗ DNA replication ↓ ⊗ Cancer cell growth / division

* s/e: (LG-STAMP)
  - L → Liver veno-occlusive disease (↑↑ clotting factor) ↓ Prevented by giving Defibrotide
  - → Leukemia (2° cancer)
  - G → GIT s/e (N, V, diarrhea)
    - ⊛ It is the MC s/e of any anticancer drug.

S → sterility (sperm & ova ↓↓)
T → Teratogenicity
A → Alopecia
M → Myelosuppresion (inhi. Bone marrow)
&
↓
MC dose limiting toxicity of any anticancer drug except: Vincristine, Bleomycin
P → Pulmonary fibrosis
(Cause destruction of type-I epithelial cells of alveoli → so reflex proliferation of type II cells & fibroblasts)

* 5 types of alkylating drugs:

(i) Nitrogen mustards
- Cyclophosphamide
- Ifosfamide

* Rx. of osteosarcoma
* s/e:
- Metabolite → Acrolein → causes hemorrhagic cystitis (inf. of bladder)

MESNA ⊖ ↗ ↓
risk of bladder cancer in future

- Cardio toxicity
- H_2O retension (sym like SIADH)
- Nephrotoxicity
- Neuro toxicity

* Other N_2 mustards
- chlorambucil (Rx: CLL)
- Melphalan (Rx: M. myeloma)
- Mechlorethamine (s/e: skin vesicles)

(ii) Nitrosoureas
- Carmustine
- Semustine
- Lomustine

* ↑ lipid soluble → Rx: CNS tumor
* s/e: Delayed and sustained myelosuppression.
- Streptozocin
* Rx: of β-cell tumor (Insulinoma)

(iii) Triazines
- Procarbazine
- Dacarbazine

* Rx: Lymphoma
- Temozolamide
* Rx: Glioblastoma multiforme

(iv) Sulfate drugs:
- Busulfan
* Rx: CML
* s/e: Adrenal suppression (Addisons disease)

2) Antimetabolites

* MOA: ⊘DNA synthesis inhibitor

Methotrexate Pemetrexed	Purine analogues Pyrimidine analogue
↓	↓
⊗ Folic acid pathway	⊗ DNA polymerase

* s/e: G-STAMP

Methotrexate

* MOA: ⊗ Dihydrofolate reductase
  ↓
  ⊗ Folic acid pathway.

* Used as
  - Anticancer (need high dose)
  - Immunosuppresant (low dose)
* DOC for choriocarcinoma
* Rx:- ALL (oral / i.v/ intrathecal)
  - Burkitt's lymphoma
  - Osteosarcoma (high dose given)
* Rx:
  - Rheumatoid arthritis
  - Psoriasis
  - IBD (inflam. bowel disease)
  - Organ transplant.
* Rx: Ectopic pregnancy (inhibit fetal cell proliferation)
* s/e:
  - Liver fibrosis
  - CNS toxicity
* Toxicity
  - Prevented by giving Folinic acid / Leucovorin/ Citrovorum factor
* Rx OC of toxicity by Forces alkaline diuresis

Pemetrexed

* Rx: Mesothelioma
* s/e: Hand & foot syndrome

purine analogues

→ 6-mercaptopurine

* Rx: ALL
* Drug is metabolized by xanthine oxidase (xo)
* Allopurinol → ⊗ XO → toxicity of drug

→ Pentostatin
→ Cladribine

* DOC for Hairy cell leukemia

Pyrimidine analogue

* - 5-fluorouracil
* Rx: ~~oral cancer~~ Colon cancer
* Metabolized in lung tissue
* s/e: ~~Head~~ Hand & foot syndrome

- Capecitabine (inactive)

* Capecitabine ⟶ 5-F.uracil
* Rx: Colon cancer
* s/e: Hand & Foot syndrome.

- Gemcitabine

* Rx: Non β-cell tumor of pancreas.
* s/e: Flu like symptoms

- Cytarabine

* Rx: ALL
* s/e: cerebellar toxicity (ataxia)

3) Anti mitotics

(i) Vinca alkaloids

- Vincristine
- Vinblastin

* Spindle formation ⊗: MOA (metaphase)
* Rx: ALL
* s/e:

B – Bone marrow suppression (rare ī vincristine)
R – Rash (hypersensi. reaction)
A – Alopecia
I – Inhibitor of spindle formation (MOA)
N – N & V, Peripheral neuropathy
S – SIADH

(ii) Taxane alkaloids

- Paclitaxel
- Docetaxel

* MOA: Over stabilisation of spindle (no spindle breakdown in early anaphase)

* Rx:
  - Breast Ca
  - Ovary Ca
  - cardiac stents (Anti fibrotic)

* s/e:

B – Bone marrow suppression
R – Rashes
A – Alopecia
N – Neuropathy, N & V
O – Overstabilization (MOA)

4) Anticancer Antibiotics

* MOA: ↑ free radicals → destroys DNA of cancer cells.
* s/e: - N & V (MC)
  - Bone marrow suppression (dose limiting toxicity)
  - pulmonary fibrosis
  - G6PD ↓↓ : Hemolytic anemia

* Drugs:
  - Anthracyclin Ab
  - Actinomycin-D

Anthracycline Ab

- Doxorubicin
- Duanorubicin
- Epirubicin

* Rx: ALL
* s/e: Cardiotoxicity
  Reduced by Dexrazoxane (Antioxidant)

Actinomycin-D

- Dactinomycin

: Rx - Ewing's sarcoma.

Mitomycin-C

- Bladder cancer
- Anorectal cancer
- Tracheobronchial stenosis (Antifibrotic)

* s/e: CHF, HUS

Bleomycin

* Rx: Testicular cancer.

5) Targeted Chemotherapy

(i) abl: bcr Tyrosine kinase ⊗ (CML)
(9:22)
- Imatinib (DOC)

(ii) HER/2 NU ⊗ (Breast Ca)
- Trastuzumab.

iii) VEGF ⊗ → ⊗ Angiogenesis
* Rx. Solid tumor (Colon Ca, RCC)
- Bevacizumab
- Ranibizumab
- Pegaptanib
* Intravitreal route (PRP)
(Proliferative retinopathy)

iv) CD-20 ⊗ → ↓ B-cell proliferation → ↓ Ab pdtn
* Rx: Lymphoma & Leukemia
- Autoimmune disorder
  - SLE
  - RA (rheu. arthritis)
  - ITP (Idio. thrombo. purpura)
* Drug is Rituximab.
* -mab ⇒ Monoclonal Ab

6) Hormonal chemotherapy (Already covered in endocrine)
- SERM
- SERD
- Aromatase ⊗
- ARB
- ↓ Testosterone
- GnRH ↑/↓

7) Miscallaneous :

i) Platinum compounds

- Cisplatin
- Oxaloplatin
- Carboplatin

* MOA & s/e ≈ Alkylating agents

Cisplatin

* Rx : Germ cell tumors (Testicular Ca, Ovary Ca)
* Rx. of Ca of reproductive tract
* Rx. of any Ca. above umbilicus
* s/e :
  - MC is N & V (maximum)
  - 2nd MC : Nephrotoxicity
    Prevented by → Amifostine
  - 3rd MC : Neurotoxicity (sensory nerve)
    (Ototoxicity)

ii) Topoisomerase inhibitor

Topo Iso. I ⊗ → - Irinotecan, - Topotecan

Topo Iso II ⊗ → - Etoposide, - Teniposide

iii) Hydroxyurea

* DOC for polycythemia vera
* DOC for thrombocytosis vera
* DOC for sickle cell anemia

iv) Asparginase (enzyme)

* Rx : ALL
* s/e : Blood clotting disturbances

v) All trans Retinoic Acid (ATRA)

* Inhibits fusion of PML & RaRα (15 : 17)
* DOC of promyelocytic Leukemia (M3 type of AML)

ANTI MICROBIALS

Anti virals

HIV

1) Fusion inhibitors

* Virus fuses with membrane of WBC via glycoprotein 41
* gp 41 is blocked by Enfuvirtide (sub. cutaneous)
* s/e : Hypersensitivity reaction

2) Entry inhibitor

* Entry in to WBC by CCR5
* CCR-5 ⊗ → Maraviroc
* s/e : Hypotension

3) Reverse transcriptase inhibitor:

* ⊗ vRNA → vDNA (v-viral) inside WBC
* Actually DNA polymerase ⊗
* DOC for HIV (best)

RTI

Nucleoside RTI (NRTI)	Non nucleoside (NNRTI) RTI
• Structure resembles nucleoside (B+S)	• Rest different from nucleoside
• Inactive form is given → (WBC cytoplasm (3 PO_4)) → Active (nucleotide)	• Always given as active form.
• Competetive inhi. of RTI	• Non comp. inhi
• effective against HIV-I & II	• only against HIV-I
• PK: Kidney elimn except - Zidovudine - Abacavir	• Liver metabolism
• s/e: i - Peripheral neuropathy ii - Lipodystrophy iii - Pancreatitis (Min s/e → Lamivudine) i, ii → max → Stavudine iii → max → Didanosine	• s/e - Hypersensi. reaction - Rash (mild) - Severe - Steven Johnson syn.

NRTI

- **Ziduvudine**
  * Safe in pregnancy
  * ↓ vertical transmission
  * s/e: Bone marrow suppresion megaloblastic anemia ↑ pigmentation of nails.
- **Lamivudine**
  * Safe in pregnancy
  * Rx. chronic Hep-B also
- **Abacavir**
  * Only NRTI with s/e hypersensitivity reaction.
- **Tenofovir**
  * Also given for chronic Hep-B treatment

NNRTI

- **Nevirapine**
  * Safe in pregnancy
  * DOC in ↓ vertical transmission
    ♀ → 200 mg stat
    Baby → 2 mg/kg/day x 6 wk
  * s/e: Liver toxicity
- **Efavirenz**
  * Unsafe to use in pregnancy.

4) Integrase enzyme inhibitor

* viral DNA integrates with human DNA → catalyzed by integrase enzyme
* ⊗ Integrase:
  - Reltegravir
  - Elvitegravir
* Rx: HIV I & II

5) Protease Inhibitor

* Viral DNA + Human DNA → hybrid vh RNA → viral protein (immature) → mature → reassembly of multiple virus → viral release.
* Immature —Protease→ Mature protein
* ⊗ Protease: (—navir)
* Rx: HIV I & II
* Liver metabolism
* Liverenzyme inhibition

Max	Min
↓	↓
Ritonavir	Saquinavir

* s/e: Lipodystrophy

max	min
Indinavir	Atazanavir
↓	
s/e renal stone	

Rx. of HIV

* K/a HAART (Highly Active Antiretroviral therapy)
* Given to any HIV ⊕ irrespective of CD4 count.
* 2 NRTI + 1 NNRTI
* Tenofovir + Lamivudine + Efavirenz
* Post exposure prophylaxis [Tenofovir + Lamivudine + Efavirenz] x 28 days.

Influenza virus

Hemaglutinase ↓⊖
- Amantidine
- Rimantidine
* Resistance is ~~no~~ present
* Outdated

Imp
Neuraminidase ↓⊖
- Oseltamivir (Tamiflu) (oral)
- Peramivir (parental)
- Zanamivir (inhalational)

↓
DOC for inf A & B virus

* Oseltamivir
↓
DOC - Swine flu (H_1N_1, H_3N_2)
DOC - Bird flu (H_5N_1)

Oseltamivir

* DOC - Swine flu (H_1N_1, H_3N_2)
* DOC - Bird flu (H_5N_1)
* Dose: 75 mg BD x 5 days
* Safe in pregnant & neonates
* No s/e.

Hepatitis virus

Hep B

- Acute Hep B
  - No antiviral
  - Symptomatic Rx.
- Chronic Hep B
  - Pegylated IF-α (interferon: IF)
  - DNA poly ⊗
    - Lamivudine
    - Adefovir
    - Tenofovir, Talbivudine
    - Entecavir (DOC)

* Lamivudine → DOC in pregnancy
* Pegylated IFα → Virus entry ⊗, (MOA) Release ⊗
  ↓
  s/e: SLE like reaction

Hep-C

1) Pegylated IF-α (same MOA)
2) Ribavirin
3) Direct protein inhibitor (NS 5A protein)
   - Ledipasvir.
4) RNA polymerase inhibitor
   - Sofusbuvir

Herpes Virus

* DOC: Acyclovir
* MOA - DNA polymerase ⊗
* Safe in pregnancy & neonates
* No s/e
* DOC for
  - HSV - I, II
  - Zoster
  - Shingles
  - EBV

Miscallenous

* CMV (Cytomegalo virus)
  - Retinitis in HIV ⊕
  - DOC: Ganciclovir
* RSV (Respiratory sensatial virus)
  - Brochiolitis
  - DOC: Palivizumab

Antifungals

1) Polyenes

* MOA : Pores in cell membrane → nutrients leaks out
* Drugs
  - Nystatin
  - Natamycin
* Local route
* As eye drops for Rx of fungal keratitis
* As mouth wash for oral Thrush
  - Amphotericin-B
* i.v route
* DOC in all serious systemic fungal infections except
  - Aspergillosis – Voriconazole
  - Coccidial meningitis – Fluconazole.
* Also DOC for Kala Azar (Visceral Leishmaniasis)
* PK : Origin → Fungus
  - $t_{1/2}$ >>> 1 week
  - Kidney elimination
* S/E : HSN reaction
  Nephrotoxicity
  Neurotoxicity
  Ototoxicity
* All s/e minimal in Liposomal Amp-B

2) Azoles

* MOA : Cell membrane ⊗ ↓ by ⊗ ergosterol synthesis in fungus CM.
  - Fluconazole (FCZ)
* DOC for Candidiasis, Coccidial meningitis
* - Intraconazole (ITZ)
* DOC for Tenia corporis, Blastomycosis, Histroplasmosis, Sporotrichosis.
  - Voriconazole (VCZ)
* DOC : Aspergillosis
  - Ketoconazole (KTZ)
* Drug s/e : ↓ testosterone synthesis
  ♂ : Erectile dysfunction, Gynecomastia.

3) Griesofulvin

* MOA : Direct DNA ⊗
* DOC : T. capitis (penetrate in keratin)
* PK – After food → T absorp
  Liver enzyme inducer.

4) Terbinafir

* MOA : cell membrane ⊗
* ∅oc : T. dingium (onchomycosis)

5) Echinocandids (i.v)

* Rx : Candidiasis
* Caspofungin, Anidulafungin

Antiprotozoal

1) Plasmodium < Vivax, Faliparum

* Anopheles ♀ mosquito → inject
(i) sporozoite → enter liver & multiply there → infection is established.

* Any medicine inhibits sporozoite are given for post prophylaxis of malaria.
  - ∅oxycycline

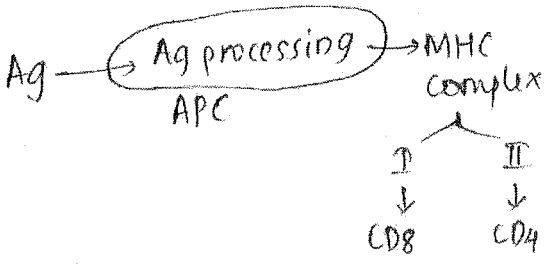
* MOA : Not known, but kills sporozoites & prevent infection.
  - Proguanil
    (∅ihydro folate reductase ⊗)
    ↓
    Folic acid pathway ⊗
  - Mefloquine } MOA not known.
  - Primaquine }

(ii) Sporozoites → merozoite → enter RBC → Schizonts now → causes C/F.
↓
Schizontocidals (used for clinical care)
↓
All antimalarials except Primaquine.

★ Chloroquine

* MOA : ⊗ ① conversion of heme in RBC to hemezoin
↓
Heme is toxic for plasmodium (Hemezoin – non toxic for plasmodium)

② Can also act on Ag presenting cells (APC)



Chloroquine prevents Ag processing → so used as immunosuppresant

Indication

1) Antiprotozoal (CQ)
- DOC: P. vivax
- Giardiasis
- Amoebiasis (liver abscess)

2) Immunosuppresant (HCQS)
- Rheu. arthritis
- DLE
- Infections (mono nucleosis)

CQ: Chloroquine
HCQS: Hydroxychloroquine SO_4

* PK → Oral route
→ Lipid solubility is high
↳ ↑↑ Vd

* S/e:
- Antiprotozoal ⊗ (no s/e)
- Immunosuppresion ↓↓ (long term)
↓
Bull's eye retinopathy

★ Quinine

* Obtained from Cinchona tree
* MOA not known
* S/e: ↓ BP, heart block, hypoglycemia
* Toxicity → High dose → Cinchonism
↓
(Tinnitus, N & V, seizure, muscle cramps)

★ Proguanil / Pyrimethamine } DHF reductase ⊗, FA pathway ⊗

* S/e: megaloblastic anemia

★ Artemesin derivatives (Chinese tree)

- Artesunate
- Artemether
- Arte ether

* MOA: ↑ free radicals → damage DNA directly. (fastest acting antimalarials)
* DOC: Cerebral Malaria (also k/a Blackwater fever)
* Safe in pregnancy
* S/e: (Free radicals)
- G6PD ↓↓ → Hemolysis

★ Miscellaneous

- Mefloquine
- Lumefantrine
- Atovaquone

iii) Gametocidals:

* When Schizonts are released from RBC → can infect other RBC → gametes → mosquito → sporozoite → salivary gland → to other human by mosq. bite

* ↓ transmission of malaria in ~~mosq~~ community.

* If Schizonts → hypnozoites (P. vivax) → Liver → again release → Relapse (property of P. vivax)

- Gametes of P. falciparum inhibited by
  - Primaquine
  - Artesunate
  - Pyrimethamine

- P. vivax
  → Chloroquine
  → Quinine

iv) ⊗ Hypnozoite (kills) / ↓ relapse
- Primaquine

* C/I in pregnancy & G6PD ↓↓

Treatment of Malaria

* National vector borne disease control programme (NVBDCP)

1) P. vivax
- Chloroquine < Schizontocidal, Gametocidal × 3 day
+
- Primaquine × 14 days
(↓ Relapse)

* In pregnant
- Chloroquine × 3 days
- No primaquine.

2) P. falciparum

Schizontocidal { Artesunate × 3 days
+
Sulfadoxine + Pyrimethamine (1 stat)
+
Gametocidal ← Primaquine (↑↑ dose) (1 stat)

* Also k/a ACT regimen (except primaquine)

* Pregnant
1st trimester → Quinine
2nd, 3rd → ACT regimen
No Primaquine

ACT regimen
Artesunate + Sulfadoxine + Pyrimethamine

3) Prophylaxis (for any foreigner coming to India)

- < 6 wks → Doxycycline → C/I in pregnant & child < 7-8 yr → Proguanil
- > 6 wks → Mefloquine → Not given to pilot (Neuro-psychiatric symptoms)

4) Complicated / Cerebral malaria

* DOC: Artesunate > Artemether > Arte-ether > Quinine.

Amoeba

* Amoebiasis
  - Intestinal amoebiasis
    - Exo
      - Tissue-A → • Metronidazole (DOC) • Quinidochlor
      - Luminal-A → • Paromomycin (DOC) • Diloxanide furoate • Dihydroemetine • Nitazoxanide
  - Extraintestinal amoebiasis → DOC: Metronidazole • Chloroquine • Doxycline

Antibiotics

Classification

(I) Cell wall inhibitors
- β-lactam → MOA: ⊗ Penicillin binding protein / or Transpeptidase ⊗
  - Penicillin (-cillin)
  - Amoxycillin
  - Ampyxillin
- Glycopeptides Antibiotics → MOA: Inhibits glycosyl transferase → Transfer of D-ala-D-ala side chain ⊗ → (W) ⊗

β-lactam
- Penicillins (-cillin)
- Cephalosporins (Cef-)
- Monobactam (Aztreonam)
- Carbapenems (-penem)

Glycopeptide
- Vancomycin
- Teicoplanin

(II) Cell membrane inhibitors
- Polypeptide Antibiotic
  - • Polymyxin-B
  - • Colistin
- Daptomycin

(III) Protein synthesis inhibitors
* Acts on ribosome (70S)

70S
- 30S → • Aminoglycosides • Tetracyclins
- 50S (SMALL-C)
  - • Streptogrammins
  - • Macrolides
  - • Lincosamides
  - • Linezolid
  - • Chloramphenicol

iv) Folic acid pathway inhibitor

* Folic acid synthase inhibitor
  - Dapsone
  - PAS
  - Sulfonamides
* DHF Reductase ⊗
  Trimethoprim

v) Nuclear material inhibitor

* DNA gyrase ⊗
  - Fluroquinolone
    (__floxacin)
* RNA polymerase ⊗
  - Rifamycins
* Direct DNA ⊗
  Nitroimidazoles
  Nitrofurantoin
  Nitazoxanide

Miscellaneous

* Ointments:
  - Fusidic acid
  - Retapamulin
  - Mupirocin
  - Framycetin

  } Protein syn ⊗

  - Bacitracin (cell wall ⊗)

* Oral
  Fosfomycin (cell wall ⊗)

PK

⇒ All cell wall inhibitors are eliminated by kidney except 2 cephalosporins (liver)
↓
Ceftriazone
Cefoperazone

⇒ 4 penicillins metabolized by liver
Cloxacillin
Oxacillin
Nafcillin
Dicloxacillin
CONDOM

⇒ On cell membrane ⊗
Polypeptide Ab, Daptomycin } Kidney elimination

⇒ Protein synthesis inhibitor
30S → Eliminated via kidney
50S → Metabolized by liver
↓
Except Doxycycline

⇒ Folic acid pathway ⊗
Synthase ⊗ : Liver & Kidney
Reductase ⊗ : Kidney

=) DNA gyrase ⊗ → Kidney except

Liver { Pefloxacin, Sparfloxacin, Moxifloxacin } PSM

=) RNA polymerase ⊗, Direct DNA ⊗ } Liver.

Que: Like which medicine is reduced in liver or kidney diseases.

- Medicines metabolized by

Liver	Kidney
1) 50S ribosome	Rest all Abtcs
2) Direct DNA ⊗	
3) RNA polym. ⊗	
4) 10 exceptions	
2 ceph	
4 pen	
1 Tetra	
3 FQ.	

PD:

* Effect of Antibiotic on bacteria

* B. static
⊗ Growth & body immune kills

1) Protein syn ⊗
- 30S, 50S except ↓
- Aminoglycosides
- Streptogrammins

2) FA pathway ⊗

Bactericidal (Kills)

↓

1) Cell wall ⊗ < β-lactam, Glycopeptide

2) CM ⊗ < PP, Daptomycin

3) Nuclear material ⊗
- DNA gyr ⊗
- Direct DNA ⊗
- RNA poly ⊗

* Bacteriostatic:
- FA pathway × < Syn ⊗, Red ⊗
except Cotrimoxazole.

* Have to give antibiotics in proper dose & proper duration (or else resistance can occur)

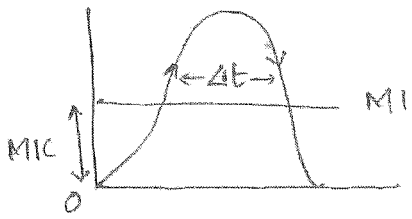
↓

Achieves Min. inhibitory conuntration (minimum conc. of AB in plasma required to inhibit ≈ 99.9% bacteria) (AB - Antibiotics)

* Pattern of inhibition:

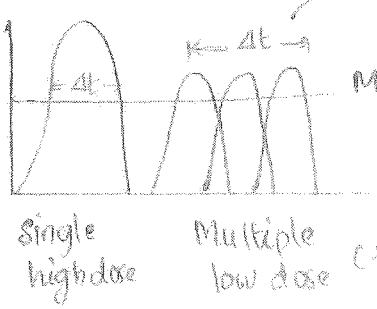
(1) Time dependent killing / inhibition
Killing ∝ Time interval for ≤ drug level remains above the MIC

- Seen in β-lactam > Glycopeptide



Δt : Time in ≤ AB conc. > MIC.

A) 100 mg



* If given in multiple low dose $\Delta t \uparrow\uparrow$ & better action.

(2) Concentration dependent killing/ inhibition

Killing $\propto C_{max}$.

* C_{max} → Maximum concentration.
* Shown by Aminoglycosides > Fluroquinolones > Azithromycin > TB drugs.
* Single high dose is preferred → max. can divide 2 dose (BDS)

(3) Post antibiotic effect (In vitro) (outside body)

⇓

* Time required by bacteria to start re-grow after removal of antibiotics from culture media
* Seen max. with Aminoglycosides then fluroquinolone

AG > FQ.

4) Resistance mechanism:

Methods

a) MC is enzyme ↑↑ production
- Enzyme will digest the antibiotic immediate, thus bacteria is saved.
- By mutation in plasmid ⊗NA
- β-lactamase against β-lactam

(b) 2nd MC → Target modification

* Modifies target on bacteria for antibiotic.
* By mutation in chromosome DNA
* β-lactam → PBP (Transpeptidase)

MCQ

↓

Modified in Staph. aureus

Also k/a MRSA (Methicillin Resistant Staph. aureus)

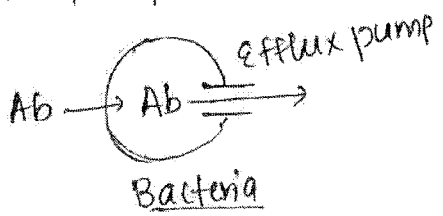
* VRSA (Vancomycin resistant Staph. aureus)

↓

Glycosyltransferase ⊗

* Rifampicin → RNA polymerase ⊗
* Fluroquinolones → DNA gyrase ⊗

(c) Efflux pump:



* Seen against
  - C → Chloramphenicol
  - E → Erythromycin
  - A → Aminoglycoside
  - T → Tetracycline.

(d) Porin channel mutation

* Porin channels are special type of channels seen in some bacteria

* Method of resistance against
  Aminoglycosides
  Fluroquinolones

(e) Modification of F. acid pathway.
  - Dapsone
  - PAs
  - Sulfonamide
  DPS

Transfer of resistance

R-gene → c help of jumping genes / transposons

- Vertical → Generation 1 ↓ to Gen. 2
- Horizontal → One colony C_1 ↓ infect → 2nd colony C_2 | by
  - Conjugation → sex pili (MC)
  - Trans duction → Bacteriophage (virus) (2nd MC)
  - Transformation → from the ext. environment it is acquired

S/e of Antibiotics

1) Cell wall (x)
   - β-lactam ↓ ⊙ Hypersensitivity reactions
     - stable - oral ↓ Replace c Macrolide antibiotics
     - unstable - i.v ↓ Give glycopeptides
   - Glycopeptide ↓ Vancomycin
     s/e ↓
     ⊙ ↑ histamine release → Vasodilatn → red rashes over skin k/a Red Man syndrome
     ⊙ Nephrotoxicity (loss of electrolyte)
     ↓
     ⊙ Sensory neuropathy (ototoxicity)

⊙ Broad spectrum antibiotic ↓ ↓ (N) gut flora ↓
- Diarrhea
- 2° infection / super infection

Pseudomembranous colitis by Clost. difficile.
- MCC is 3rd Gen Ceph > Clindamycin

Doc for P. colitis: Vancomycin > Metranidazole

β-lactam s/e

- All β-L → Kidney elimination
  If CRF → ↑ Accumul° → Seizures
- Ampicillin → Viral infection
  ↓
  Morbiliform Rashes
  (infectious mononucleosis)
- Cephalosporins
  Cefoxitin, Cefotetam, Cefmetazone } Vit K ↓↓ (Bleeding)
- Cefoperazone, Cefoxitin } ⊕ Alcohol → ↓ Disulfiram like reactions.

2) Cell membr. ⊗ s/e → No need

3) P.S ⊗
   30 S ⊗ – s/e ~~need~~.

Aminoglycosides s/e

a) Nephrotoxicity (Max: Gentamycin)

b) Ototoxicity ← Cochlea (Base > Apex)
   Vestibule

- Base → high frequency sound.
- Max. cochlear toxicity by Amikacin
- Max. vestibule toxicity by Streptomycin.

c) NMJ ⊗ → muscle weakness
   → c/I M. gravis
   Max. → Gentamycin

d) Teratogenic → Inner ear defects (Cochlea ↓↓)
   C/I in pregnancy.

e) Given i.v (always) → also k/a injectable
   iv → Pain & sepsis @ site of infection.

Tetracyclin s/e

i) Ca^{2+} binding ← Bone, Teeth } ↓ growth
   C/I in pregnancy.
   C/I in children < 7-8 yrs

ii) Minocycline, Demeclocycline } Photoxic Rxn
   ↓
   ↑ skin pigmentation

iii) Tetracycline → Liver toxicity
   ← ↑ ICT
   Also k/a → (pseudo tumor cerebri)

iv) Expired tetracyclin →
   Fanconi's anemia

50S s/e (SMALL-C)

(1) Streptogramins
- Myalgia, Arthralgia

(2) Macrolides - Diarrhea

(3) Lincosamide - Broad spectrum Ab
↓
Diarrhea, 2° infection

(4) Linezolid - Bone marrow suppression,
↓ platelet count, Ant. uveitis

(5) Chloramphenicol -
- BM suppression (max by them)
- When given to neonate → colour changes to grey k/a Grey baby syndrome.
- Broad spectrum → 2° infection.

4) ~~Sulfonamides s/e~~ F.A ⊗ s/e

Sulfonamide

1) HSN Rx
2) Bone marrow suppression
3) ↑ Bilirubin ↔ Jaundice, Kernicterus
4) G6PD deficiency → Hemolysis
5) Crystalluria (Deposit in kidney)

5) Nuclear material ⊗

* Fluroquinolone

+ ↑ epilepsy (C/I in known case of Epilepsy)
+ Tendinitis (↓ growth of tendon)
C/I in neonates & children
C/I in pregnant.
+ Phototoxicity
+ Hypoglycemia

Nitroimidazole:

+ Metronidazole → N & V, Metallic taste
- When given ± alcohol → disulfiram like reaction

Indications of Antibiotics

Cell wall ⊗

β-lactam AB:

1) Penicillin
a) • Penicillin-G is first discovered by Alexander Flemming.
• Pen-G is effective against
G+ve < Cocci, Bacilli
G-ve → Cocci
Anaerobic
• But not against G-ve bacilli

bacterioides, mycoplasma.

- Pen-G is DOC for P-GLASSS
  - Pneumococcus
  - Actinomycetes
  - Streptococcus
  - Gas gangrene (Cl. perfringens)
  - Leptospirosis (Leptospira)
  - Syphilis (T. pallidum)
  - Spirillum minor bacteria (rare, responsible for rat bite fever)

b) 5 penicillin — CONDOM
- Cloxacillin
- Oxacillin
- Naficillin
- D & Dicloxacillin
- O
- Methicillin

- Methicillin was withdrawn due to interstitial nephritis
- Spectrum → Pen G ⊕ → DOC for β lactamase producing staph. aureus

c) Extended spectrum penicillin
* Spectrum → Pen G ⊕ g-ve bacilli
* Broad spectrum AB.
* 1st 2 : Ampoxillin & Ampicillin

↓

Useful against all G-ve bacilli except pseudomonas.

* Ampicillin is DOC for
  - Listeria
  - Enterococcus.

* Others - Carbencillin, Azlocillin, Mezlocillin, Pipracillin

↓

Effective against Pseudomonas (Antipseudomonal penicillin)

2) Cephalosporin:

Gen-I

* Against only G+ve < Cocci / Bacilli

i) Cephalexin
ii) Cefadroxil
iii) Cefazolin → MC used AB for Sx prophylaxis

↓

Given i.v (just before incision)

Gen II

* Against G+ve < G-ve
* i) Cefoxitin, Cefotetan, Cefmetazole, Cefuroxime } Give against Anaerobic Bacteria

Gen III

* G+ve <<<< G-ve

i) Ceftazidime } against Pseudomonas
ii) Cefoperazone } (DOC-ceftaxidime)

(iii) Cefixime
DOC → STD by Gonococcus

(iv) Ceftriazone
- DOC for systemic infection caused by Gonococcus.
- Empirical DOC (Tout confirm diagnosis) in Typhoid, Meningitis, CNS abscess, Endocarditis

(v) Cefotaxime
- DOC for Meningitis by Meningococcus & H. influenza

(vi) Cefpodoxime

vii) Cefomondole

Gen IV

* Effective against all G+ve, All G-ve, Pseudomonas
* Broad spectrum AB
* Cefipime (-pi-)
Cefipirone

3) Monobactams:

Aztreonam

* Against Pseudomonas, β-lactamase producing Staph. aureus.

4) Carbapenems

- Imipenem
  - Inhibited by peptidase enzyme in kidney.
  - Peptidase is inhibited by Cilastatin.
- Doripenem
- Meropenem

- All are broad spectrum AB
- All G+ve, G-ve, Pseudomonas, Anaerobes.

Staph. aureus

* DOC : Pen-G
* Pen-R → CONDOM
β-lactamase (+)
* [Pen-R (PBP)] MRSA → Vancomycin
* VRSA → Daptomycin

Pseudomonas

1) β-lactams
   - Pen → Extended spectrum P
   - Ceph (Gen III, IV only)
   - MB (All)
   - Carbapenem (All)

except ← Amoxicillin & Ampicillin.

- Gen III → DOC: Ceftazidine

2) Aminoglycosides
   - Tobramycin
   - Amikacin
   - Gentamycin

3) FQ → Ciplox

4) Polypeptide AB → All

Syphilis

* DOC → Penicillin G in 3 forms

- Aqueous Pen-G → $t_{1/2}$ <<< → fast onset → used in acute emergencies
- Procaine Pen-G → Intermediate $t_{1/2}$ & onset → used as alternative of Bz
- Benzathine Pen-G → $t_{1/2}$ >>> → slow onset → Maintanence Rx.

* Syphilis → 1°, 2°, 3° Syphilis
* 3° syphilis → 3 types
   - Benign
   - Cardiac
   - Neuro (meningitis)
* 1°, 2°, Benign, Cardiac → Stable patients

Benzathine Pen-G > Procaine Pen-G.

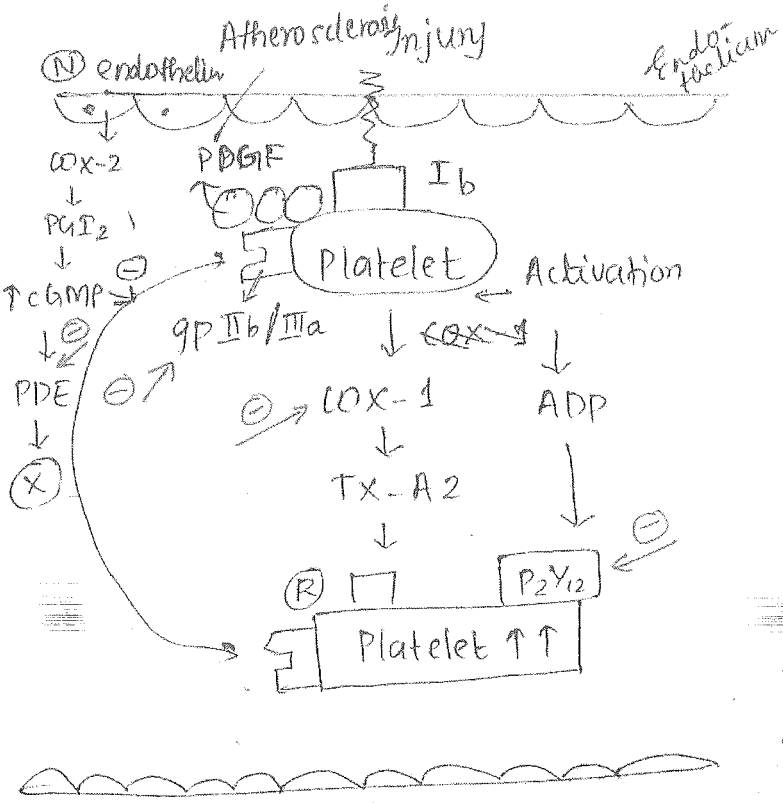
1° → single dose (2.4 million unit)

* Neuro → Aqu. Pen-G > Procain. Pen-G
* Pen-G HSN Rx → DOC: Doxycycline.

HEMATOLOGY

Antiplatelet drugs

* Drugs → ↓ platelet aggregation → ↓ Atherosclerosis.
* Arteries obstruction (used in)
* Indication:
   1) Angina
   2) STEMI
   3) Cerebral stroke
   4) Gangrene



* COX-1 is inhibited by
  - Aspirin (Given in lowdose)
* P_2Y_{12} inhibited by
  - Clopidogrel
  - Ticlopidine
  - Prasugrel
* gp IIb / IIIa inhibitor
  - Abciximab
  - Tirofiban
  - Eptifibatide
* PDE inhibitor
  - Dipyridamole
  - Cilastazol

COX-1 ⊗

* Aspirin (75 → 325 mg dose)
  if > 325 mg → ⊗ COX-2
* Aspirin is 1st drug given in MI

{ [Angina → 1st drug: NTG
CHF → " : Furosemide
MI → " : Aspirin] }

* Aspirin → Oral, chew (no bitterness)
* Aspirin is irreversible inhibitor of COX-1 ↓
* Platelet → cannot form new COX-1 → because platelets are devoid of nucleus → after 7 days this platelet is removed (life span) → so action is long lasting
* But Aspirin $t_{1/2}$: 6-8 hrs (short)

⇓

Hit & Run phenomenon.

* Aspirin is given once daily.
* S/E:
  - Gastritis
  - Peptic ulcer disease
  - HSN Rxn (Hypersensitivity reaction)

P_2Y_{12} ⊗

Clopidogrel

* Given as prodrug → activated by CYP_2C19 enzyme (liver)
* PPI (Ome2) inhibits CYP_2C19.

$gpII_bIII_a$ ⊗

* Most efficient antiplatelet
* Given i.v route.

PDE ⊗

* Dipyridamole → s/e Coronary steal phenomenon
  (outdated) ↓
  diverted from ischemic to non-ischemic area
* Dipyridamole
  Isoflurane.

Anticoagulants

* Clotting factor pathway ⊗
* In venous obstruction
* Indications:
  1) DVT (Deep vein thrombosis)
  2) Pulmonary embolism
  3) Cerebral stroke
  4) STEMI
  5) Atrial Fibrillation
  6) After major joint Sx.
  7) DIC
* Group of medicines:

I) Factor Xa ⊗

* Parenteral (i.v or s.c)
* Unfractionated heparin (UFH)
* Low molecular weight Heparin (LMWH)
* UFH → ⊗ Xa > IIa
  LMWH ⇒ ⊗ Xa
* MOA: ↑ activation of AT-III enzyme → ↑ anti Xa protein → ⊗ Xa
* Properties:
  → ⊗ cross placenta → Doc ↑ coagulopin
  → ↑↑ lipoprotein lipase → ↓ TG in plasma.
  → origin: Pig intestine / ox lung (mast cells) ↓ Heparin.
* s/e:
  - Hyperkalemia
  - Osteoporosis
  - Alopecia
  - ↓ platelet (HIT syndrome)

HIT: Heparin Induced Thrombocytopenia.

* Toxicity: Bleeding

Antidote → Protamine sulfate of Heparin toxicity (i.v)

Monitoring → aPTT (maintain dose acc. to aPTT, prevents toxicity)

* eg: of LMWH
  - Enoxaparin (-parin)
  - Dalteparin

* UFH present as such (generic form)

II Xa (x) Oral
  - Apixaban
  - Rivaroxaban

* Monitoring → aPTT
* Toxicity → Antidote is FFP (Fresh frozen plasma)

III IIa (x)

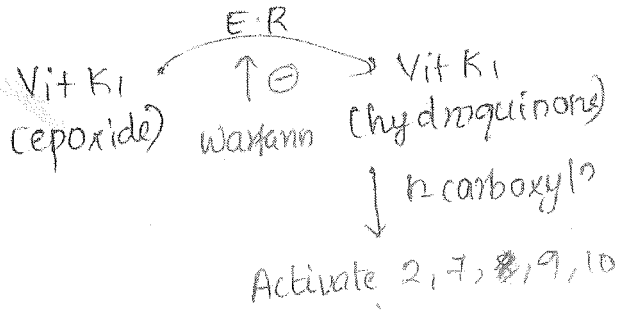
* IIa is Thrombin
* Direct thrombin inhibitor
  - Lepirudin
  - Bivalirudin
  - Argatroban

  } obtained from Leech saliva

* Also inhibitor of common clotting pathway. So need aPTT monitoring.

IV Vit K dependent CF (x)
(2, 7, 9, 10)

* MOA: Epoxide reductase enzyme inhibitor → which is required for converting Vit K1 epoxide form to Vit K1 (hydroquinone) form.



* Properties of Warfarin
  - Oral route
  - Slow onset (2-3 days) (used in maintanence Rx)
  - ↑↑ Acidity (97% Albumin)
  - t½ → 36 hrs
  - Liver metabolism (CYP2C9) (zero order kinetics)
  - Placenta (cross) → teratogenic
    ↓
    Contradi's syndrome (in baby)
    (chondrocytes never develop
    Saddle nose ... dl,

stippled epiphysis, dwarfism

* Monitoring : INR
(International Normalized Ratio)

$$INR = \left[\frac{PT\ (patient)}{PT\ (standard)}\right]^{ISI}$$

PT - Prothrombin time

- (N) INR = 1
- Toxicity of Warfarin occurs when INR > 4.5
- Antidote is Vit K_1 (slow onset)
- If bleeding Vit K_1 + FFP (fresh frozen plasma)

Thrombolytic / Fibrinolytic

* $\bar{X}a \rightarrow IIa \rightarrow \underline{Ia}$ (fibrin clot) ← (−)

* MOA : ↑↑ t-PA (tissue plasminogen activator)

Plasminogen —tPA→ Plasmin → dissolve clot

* Indication :
  1) STEMI
  2) Cerebral stroke
  } Acute episode

* Golden time period in STEMI within 3 hrs (uptill 12 hrs)

Drugs

Specific	Non-specific
(dissolve only pathological clot)	(Patho. + phys. clot dissolved)
↓	↓
- Tenecteplase	- Streptokinase (from Streptococcus)
- Reteplase	↓
- Alteplase	s/e: HSN Rxn
	- Urokinase (from human urine)
	No HSN Rxn

* C/I :
  1) H/O Hemorrhagic stroke
  2) HTN crisis
  3) Ongoing bleeding (Bleeding peptic ulcer)
  4) H/O neuro surgery

↓

Rx : ~~PCA~~ PCA (Percutaneous Angioplasty)

Hypolipidimic drugs

* Rx. of hyperlipidemia

(N) HMG CoA reductase (X)

* SOA : Liver
* ↓ cholesterol levels
* Statins → (X) HMG CoAR

- Rosuvastatin (R>A)
- Atorvastatin

* Cholesterol is needed for steroid hormone, bile acid.
+ So liver consumes cholesterol in LDL for steroid & BA synthesis
↓
Thus cholesterol ↓ in LDL.

* DOC in
- Hyperlipidemia
(Best given during evening and night time → because cholesterol syn. in that time)

PK
+ Oral
* Liver metabolism (CYP3A4)
+ C/I in pregnancy

S/E
* Liver toxicity (LFT monitoring)
+ Myopathy (CPK monitoring)
* Weight loss
* Dry skin

2) Fibrates

* SOA: Endothelium of blood vessels
* MOA: Activate PPAR-α Receptor
↓
↑ lipoprotein lipase
↓
↑ TG breakdown
so ↓ VLDL (TG max in VLDL)

* - Gemfibrozil
- Fenofibrate
- Clofibrate

+ S/E ≈ Statin.

3) Miscallaneous

a) Ezetimibe
• Inhibits cholesterol absorption from small intestine.

b) Vit B_3 (Niacin)
- ↑ HDL

c) Bile acid binding drugs
• ↓↓ cholesterol in the plasma
- Colesevalam
- Cholestyramine
- Colestipol.

d) Herbal drugs
- Gugulipid
- Garlic extract.

• Thrombolytic drugs → Toxicity
→ Bleeding; Rx DOC - ↓ t-PA
DOC (1) EACA (Epsilon Amino Caproic Acid)
(2) Tranexamic acid (in Menorrhagia)
(3) Aprotinin