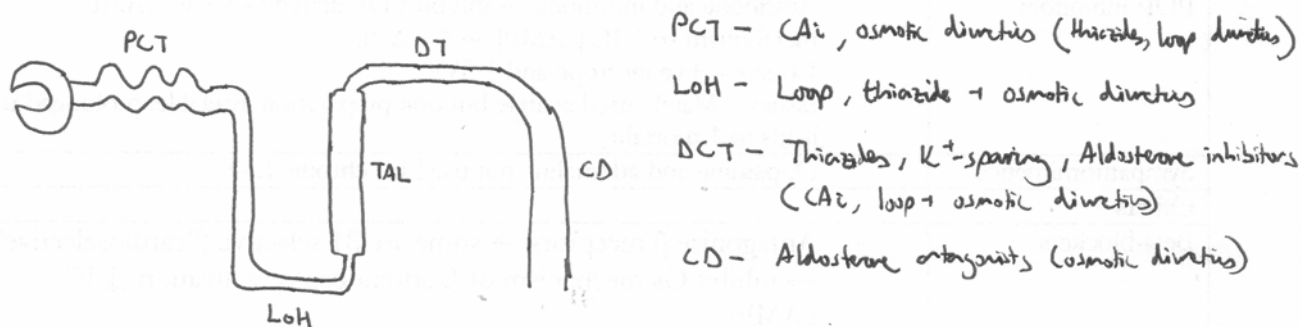


DIURETICS

- To outline a physiological basis of classifying diuretics related to their site of action.
- To describe the actions of mannitol, frusemide, thiazides, aldosterone antagonists and carbonic anhydrase inhibitors.
- To outline the side-effects of the diuretics.
- To describe the major applications and toxicities of thiazides, loop diuretics and potassium-sparing diuretics.

Sites of diuretic action:



Effect of diuretics on urine:

Diuretics	Volume	pH	Na^+	K^+	Cl^-	HCO_3^-
Thiazide diuretic	+++	↑	↑↑	↑	↑	↑↑
Loop diuretic	++	↓	↑↑	↑	↑	-
Osmotic diuretic	+++	-	↑	-	↑	↑
K^+ -sparing diuretic	+	↑	↑↑	-	↑	↑↑
Carbonic anhydrase inhibitor	+	↑↑↑	↑	↑↑	↓	↑↑↑↑

(I) Thiazide diuretics:

Example: Hydrochlorothiazide, Chlorthiazide, Indapamide (all related to sulphonamides)

Mechanism of action:

- Inhibits Na^+/Cl^- cotransporter in early DCT and cortical portion of TAL of LoH (minor effect at PCT) → ↓ Na^+ reabsorption (a/w ↓ H_2O reabsorption) and ↓ Cl^- reabsorption
- In late DCT → ↑ K^+ and H^+ excretion due to ↑ Na^+/H_2O delivery (alters transtubular electrical potential)
- Potent diuretic → produces hypokalaemic, hypochloraemic metabolic alkalosis

Effect on urine composition:

Volume	pH	Na^+	K^+	Cl^-	HCO_3^-
+++	↑	↑↑	↑	↑	↑↑

Pharmacokinetics:

- Generally have well-absorbed orally (↑ bioavailability) and renally excreted
- Differences b/t thiazide diuretics lie with → rate of oral absorption (due to different lipid solubility), rate of onset and duration of action (due to renal tubular handling of drug)

Clinical uses:

- (1) Treat essential HTN
 - o Mechanism – ↓ ECFV and C.O. due to diuresis/natriuresis (initially), and peripheral vasodilation due to ↓ SNS activity on VSMC (weeks later)
 - o Generally combined with other anti-HTN agents → reduces their dosage and minimise their S/E
- (2) Mobilise oedema a/w renal, hepatic, cardiac dysfunction → due to diuresis
- (3) Treat diabetes insipidus → ↑ CD sensitivity to ADH
- (4) Treat hypocalcaemia → due to ↓ renal Ca^{2+} excretion
- (5) Treat renal tubular acidosis → due to metabolic alkalosis

Side-effects:

- (i) Hypovolaemia → causing hypotension
- (ii) Electrolyte disturbances:
 - o Hyponatraemia
 - o Hypokalaemia → causes cardiac arrhythmias, muscle weakness, GI ileus, digitalis toxicity, potentiates ND NMBD effect (Nb. concurrent use of K^+ -sparing → can be used to prevent hypokalaemia)
 - o Hypochloraemia
 - o Hypomagnesaemia → cardiac arrhythmias
 - o Hypercalcaemia (due to ↓ Ca^{2+} excretion)
- (iii) Cardiac arrhythmias → due to electrolyte disturbances
- (iv) Metabolic alkalosis
- (v) Hyperglycaemia, which can aggravate DM → due to inhibition of pancreatic insulin release, ↓ glucose utilisation peripherally (↓ glycogenesis/↑ glycogenolysis)
- (vi) ↑ plasma cholesterol/TAG levels
- (vii) Hyperuricaemia, which can exacerbate gouty arthritis → due to renal transporter competition b/t urate and thiazide for secretion
- (viii) Renal and hepatic dysfunction → due to ↓↓↓ organ blood flow
- (ix) Rarely: Rash, blood dyscrasias (aplastic/haemolytic anaemia, leucopaenia, agranulocytosis, thrombocytopenia), photosensitivity, impotency

(II) Loop diuretics:

Example: Frusemide (sulphonamide derivative)

Mechanism of action:

- Inhibit NKCC1 co-transporter in medullary portion of TAL of LOH (main effect) → ↓ Na^+ , K^+ and Cl^- reabsorption → ↓ medullary hypertonicity → impairs counter-current multiplier system (or urinary concentration) → ↓ H_2O reabsorbed in CD
- Also ↓ Na^+ / Cl^- reabsorption in cortical portion of TAL of LoH, PT and early DCT (minor)
- Moderately potent diuretic:
 - o Responsiveness directly related to GFR over a wide range
 - o Causes renal vasodilation (due to renal production of PGs) → ↑↑↑ RBF and redistributes it from inner to outer renal cortex → promotes diuretic effect
 - o If given IV → effect within 2-10 mins and lasts 2 hrs; if given PO → effect within 1 hr and lasts 4-6 hrs

Effect on urine composition:

Volume	pH	Na^+	K^+	Cl^-	HCO_3^-
++	↓	↑↑	↑	↑	-

Pharmacokinetics:

Absorption	PO (65% bioavailability) or IV
Distribution	90% protein binding (binds albumin only)

Metabolism/ Elimination	- Renal glucuronidation → 80% excreted in urine (unchanged and metabolites); 20% in faeces - Elimination $t_{1/2} < 1$ hr
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Clinical uses:

- (1) Mobilise oedema fluid due to renal, hepatic, cardiac dysfunction → due to diuresis
- (2) Treat ↑ ICP
 - o Mechanism – Due to systemic diuresis, ↓ CSF production (interferes with Na^+ transport in glial cells), ↓ cerebral oedema (↑ H_2O transport out of neurons)
 - o Not as effective as mannitol → BUT can be combined with it to be more effective at ↓↓ ICP (but risk of severe dehydration/electrolyte issues)
 - o Does not require intact BBB (cf. mannitol)
- (3) Treat symptomatic hypercalcaemia → due to ↑ Ca^{2+} excretion
- (4) Treat ARF (converts oliguric RF to non-oliguric form) → controversial
- (5) Treat essential HTN (rarely) → produces peripheral vasodilation (like thiazides) but ↓ intravascular fluid occurs too rapidly (evokes BRR response and ↑ SNS activity that ↑ BP)

Side-effects:

- (i) Hypovolaemia → causing hypotension
- (ii) Electrolyte disturbances:
 - o Hyponatraemia
 - o Hypokalaemia → causes cardiac arrhythmias, muscle weakness, GI ileus, digitalis toxicity, potentiates ND NMBD effect (Nb. concurrent use of K^+ -sparing → can be used to prevent hypokalaemia)
 - o Hypochloraemia
 - o Hypomagnesaemia → cardiac arrhythmias
 - o Hypocalcaemia (due to ↑ Ca^{2+} excretion)
- (iii) Metabolic alkalosis
- (iv) Hyperuricaemia, hyperglycaemia and ↑ plasma TAG/cholesterol (like thiazides) → BUT less significant
- (v) Nephrotoxicity → due to ↑ renal tissue [] of nephrotoxic drugs (Ie. aminoglycosides), and/or allergic interstitial nephritis
- (vi) ↓ renal clearance of Lithium
- (vii) Ototoxicity → esp with prolonged use, high doses, concurrent use of other ototoxic drugs (esp aminoglycosides), and renal failure
- (viii) Allergic reaction (due to cross allergy to sulphonamide nucleus)
- (ix) Tolerance → acute (due to $\text{Na}^+/\text{H}_2\text{O}$ retention a/w RAAS activation 2° to a contracted ECFV) and chronic (due to compensatory renal tubular hypertrophy (esp DCT))

(III) Osmotic diuretics:

Example: Mannitol (6-C sugar; polyhydric alcohol)

Mechanism of action:

- In kidneys:
 - o Completed filtered at glomerulus and is not absorbed within renal tubules → causes ↑ tubular fluid osmolality → prevents H_2O reabsorption (esp at proximal renal tubules and LoH, which have very ↑ H_2O permeability) → promotes osmotic diuresis → ↑ urine volume
 - o Washes out medullary interstitial gradient → ↓ CCM system (and urine concentrating ability)
 - o ↓ electrolyte absorption (Na^+ , Cl^- , K^+ , HCO_3^-) → as they are diluted in H_2O
- Also ↑ plasma osmolality → creates osmotic gradient that draws H_2O from ICF to ECF (Ie. from brain) → IVV expansion (Ie. ↑ RBF, ↑ preload)
- Effect within 10-15 mins and lasts for 2 hrs

Effect on urine composition:

Volume	pH	Na ⁺	K ⁺	Cl ⁻	HCO ₃ ⁻
+++	-	↑	-	↑	↑

Pharmacokinetics:

Absorption	Available parentally only (not absorbed orally)
Distribution	Remains within intravascular space
Metabolism/ Elimination	- Nil metabolism → cleared entirely via kidneys (filtered only) - Elimination t _{1/2} 100 mins

Clinical uses:

- (1) Prophylaxis against ARF (“renoprotective”) a/w cardiovascular surgery, transplant surgery, surgery a/w jaundice, and nephrotoxins (rhabdomyolysis, haemolytic transfusion reactions) → 2° to ↑ RBF → but controversial evidence
- (2) Treat ↑ ICP
 - Mechanism – Shifts fluid out of brain (due to ↑ plasma osmolarity) and ↓ CSF volume (due to ↓ CSF formation)
 - Intact BBB required → otherwise mannitol enters brain and causes rebound cerebral oedema
 - ↓ effect with chronic use → b/c brain adapts to ↑ plasma osmolarity
- (3) Short-term reduction in IOP for eye surgery/glaucoma treatment → ↓ aqueous humour due to ↑ plasma osmolarity
- (4) Differentiate b/t causes of acute oliguria → if U/O ↑, then oliguria caused by low IVV (otherwise, due to renal dysfunction)

Side-effects:

- (i) Fluid disturbances → initially ↑ IVV (risk of APO in pts with LVF due to ↑ preload); later IVV depletion due to dehydration
- (ii) Electrolyte disturbances (↓ Na⁺, K⁺)
- (iii) Plasma hyperosmolarity
- (iv) Renal toxicity (toxic to CD/DCT)
- (v) Irritant to tissues/veins
- (vi) Allergies (rare)

(IV) Potassium-sparing diuretics:

Example: Amiloride (pyrazinoylguanidine) and Triamterene (pteridine)

Mechanism of action:

- Inhibits Na⁺/K⁺ exchange in DCT (independent of aldosterone) → ↓ Na⁺ reabsorption (a/w ↓ H₂O reabsorption) and ↓ K⁺ excretion
- Weak diuretic → amiloride is more potent than triamterene

Effect on urine composition:

Volume	pH	Na ⁺	K ⁺	Cl ⁻	HCO ₃ ⁻
+	↑	↑↑	-	↑	↑↑

Pharmacokinetics:

Absorption	Available in oral form only → Amiloride is partly absorbed (50% bioavailability), while Triamterene is readily absorbed (↑ bioavailability)
Distribution	Amiloride has minimal protein binding (< 5%)
Metabolism/ Elimination	Amiloride: Not metabolised, excreted unchanged in urine and faeces → elimination t _{1/2} 18 hrs Triamterene: Extensively metabolised (with active metabolites)

Clinical uses:

- (1) Treatment of HTN → due to diuresis
- (2) Oedema of cardiac, renal, hepatic origin → due to diuresis
- (3) Used in combination with loop or thiazide diuretic → augments diuresis while offsetting opposing effects on renal excretion of K^+

Side-effects:

- (i) Hyperkalaemia (main side-effect) → esp in context of renal failure, or drugs that ↑ plasma $[K^+]$ (Eg. ACEi, A2RB, Etc.)
- (ii) Hypovolaemia
- (iii) Hyponatraemia (minimal)
- (iv) Hyperglycaemia (minimal)
- (v) Other side-effects are rare (such as GI upset (N/V, pain, diarrhoea), rash, interstitial nephritis, haematological disturbances)

(V) Aldosterone antagonists:

Example: Spironolactone (synthetic steroid → resembles structure of aldosterone)

Mechanism of action:

- Binds to cytoplasmic mineralocorticoid receptor at principal cell of CD and DCT → competitive antagonist to aldosterone (and hence, only effective when aldosterone is present) → ↓ Na^+ and Cl^- reabsorption (a/w ↓ H_2O reabsorption), and ↓ K^+ excretion
- Weak diuretic (as only 2% of tubular Na^+ absorption is controlled by aldosterone)
- Delayed effect (2-4 days for onset/offset) → b/c it inhibits aldosterone-receptor complex from migrating into nucleus to activate gene expression

Pharmacokinetics:

Absorption	Available in oral form only (70% bioavailability)
Distribution	Extensive protein binding (>90%)
Metabolism/ Elimination	- Rapid and extensive hepatic first-pass metabolism (such that none is excreted in urine unchanged) → to canrenone (active metabolite) → then canrenoate (inactive metabolite) → then metabolites renally excreted - Elimination $t_{1/2}$ 1-2 hrs

Clinical uses:

- (1) Treat refractory oedematous states a/w hyperaldosteronism (esp CCF, liver cirrhosis, nephrotic syndrome)
- (2) Treat 1° hyperaldosteronism (Conn's)
- (3) Treat HTN → similar effects to a thiazide diuretic
- (4) Used in combination with a loop or thiazide diuretic → augments diuresis while offsetting opposing effects on renal excretion of K^+

Side-effects:

- (i) Hyperkalaemia (main side-effect) → esp in context of renal failure, or drugs that ↑ plasma $[K^+]$ (Eg. ACEi, A2RB, Etc.)
- (ii) Hypovolaemia
- (iii) Hyponatraemia
- (iv) Anti-androgenic effect → gynaecomastia (men) and menstrual irregularity (women)
- (v) GI disturbances (esp N/V)

(VI) Carbonic anhydrase inhibitors:

Example: Acetazolamide (sulfonamide class)

Mechanism of action:

- Non-competitive inhibition of luminal and brush border carbonic anhydrase in PCT (minor effect in DCT also) – Inhibits $\text{CO}_2 + \text{H}_2\text{O} \rightarrow \text{H}_2\text{CO}_3 \rightarrow \text{H}^+ + \text{HCO}_3^-$
- Weak diuretic $\rightarrow$ produces alkaline urine and hyperchloraemic metabolic acidosis
 - o $\downarrow \text{H}^+$ produced by CA $\rightarrow$ leads to $\downarrow \text{H}^+$ secreted by Na^+/H^+ exchanger $\rightarrow$ leads to (i) $\downarrow \text{Na}^+$ reabsorption (a/w $\downarrow \text{H}_2\text{O}$ absorption) and (ii) $\downarrow \text{HCO}_3^-$ reabsorption
 - o $\uparrow \text{Na}^+/\text{H}_2\text{O}$ load in distal tubule alters transtubular electric potential difference $\rightarrow$ leads to $\uparrow \text{K}^+$ secretion
 - o $\uparrow$ reabsorption of Cl^- $\rightarrow$ to maintain ionic balance a/w HCO_3^- loss

Effect on urine composition:

Volume	pH	Na^+	K^+	Cl^-	HCO_3^-
+	$\uparrow\uparrow\uparrow$	$\uparrow$	$\uparrow\uparrow$	$\downarrow$	$\uparrow\uparrow\uparrow\uparrow$

Pharmacokinetics:

Absorption	PO, (95-100% bioavailability), IV or topical (eye drops)
Distribution	Highly protein bound (70-90%)
Metabolism/ Elimination	- Not metabolised $\rightarrow$ excreted unchanged by kidneys within 24 hrs - Elimination $t_{1/2}$ 2-6 hrs

Clinical uses:

- (1) Prevent and treat altitude sickness $\rightarrow$ metabolic acidosis counteracts respiratory alkalosis
- (2) Treat glaucoma $\rightarrow$ $\downarrow$ aqueous humour production ($\downarrow$ IOP)
- (3) Treat petit mal epilepsy $\rightarrow$ $\downarrow$ seizure activity due to $\uparrow \text{CO}_2$ and metabolic acidosis
- (4) Treat Meniere's disease
- (5) $\downarrow$ ICP $\rightarrow$ $\downarrow$ CSF formation
- (6) Manage familial periodic paralysis $\rightarrow$ metabolic acidosis $\uparrow\uparrow\uparrow [\text{K}^+]$ in skeletal muscle
- (7) Treat metabolic alkalosis in critically ill patient $\rightarrow$ by metabolic acidosis
- (8) Stimulate ventilation in patients with metabolic alkalosis $\rightarrow$ due to metabolic acidosis and $\uparrow \text{CO}_2$ produced

Side-effects:

- (i) Hypovolaemia
- (ii) Hyponatraemia
- (iii) Hypokalaemia
- (iv) Exacerbate respiratory acidosis in pts with COPD
- (v) Rarely: GI/haematological disturbances, rash, renal stones

ADRENORECEPTOR BLOCKING AGENTS

- (a) *To explain mechanisms and physiological consequences of alpha 1, alpha 2, beta 1 and beta 2 receptor blockade.*
- (b) *To classify alpha and beta receptor blocking agents according to their pharmacokinetic and pharmacodynamic properties.*
- (c) *To describe the pharmacology of alpha receptor blocking agents and apply this to their clinical use.*
- (d) *To describe the pharmacology of beta blockers with particular reference to propranolol, atenolol, metoprolol, esmolol, carvedilol, sotalol, labetalol.*
- (e) *To describe the clinical uses of beta receptor blocking agents and their potential adverse effects.*

α -Adrenoceptor Antagonists:

“ α -adrenoceptor antagonists”:

- Bind selectively to α -adrenergic receptors (either α_1 or α_2 , or both types) → prevent catecholamines or other sympathomimetics from provoking an α response
- Most are competitive antagonists (except phenoxybenzamine)

Remember – α -adrenoceptor response:

- Post-synaptic
 - o α_1 (GPCR; Gq) – Peripheral vasoconstriction, mydriasis, salivation, uterine and prostatic SM contraction, ejaculation, hepatic glycogenolysis
 - o α_2 (GPCR; Gi) – Platelet aggregation, hyperpolarisation of CNS neurons, ↓ insulin release from beta-pancreatic islet cells
- Pre-synaptic
 - o α_2 (GPCR; Gi) – Inhibit nerve terminal NAd release

(I) Non-selective α -adrenoceptor antagonists:

Phentolamine:

- Structure – Substituted imidazolone derivative
- Presentation and dosing – Clear pale-yellow solution of phentolamine mesylate (10 mg/mL) → given IV 1-5 mg (titrated to effect), with effect in 1-2 mins and lasting 10-15 mins
- Clinical uses:
 - o (i) Treat acute hypertensive crises due to pheochromocytoma (esp with tumour manipulation), excessive sympathomimetics, and MAOi reactions with tyramine
 - o (ii) Treat LVF complicating MI
 - o (iii) Assess SNS-mediated chronic pain
 - o (iv) Formerly used to treat pulmonary HT
- Mechanism of action – Competitive non-selective α -blocker (postsynaptic α_1 and presynaptic α_2 receptors) → ↑ affinity for α_1 than α_2 receptors (by 3-5 X)
- Pharmacokinetics:

Absorption	Mainly IV route (rarely PO → 20% bioavailability)
Distribution	50% bound in plasma protein
Metabolism/ Elimination	- Extensive hepatic metabolism (only 10% excreted unchanged in urine) - Elimination $t_{1/2}$ 20 mins

- Pharmacodynamic effects:

CVS	- α_1 antagonist effects: - o ↓ SVR (due to peripheral vasodilation) → ↓ BP - o Indirectly ↑ C.O. due to ↑ HR/↑contractility a/w BRR triggered by ↓ BP - o ↓ PVR and PAP (due to pulmonary arteriolar dilation) - o ↑ coronary blood flow (due to coronary dilation) - α_2 antagonist effects: - o Further ↑ C.O. due to ↑ HR/↑contractility a/w BRR (due to enhanced nerve terminal NAd release)
Side-effects	- α_1 antagonist side-effects: - o Orthostatic hypotension and dizziness - o CNS symptoms (esp lethargy, sedation/drowsiness, headaches, vertigo) - o Nasal congestion → due to dilated nasal mucosal vessels - o Fluid retention (needing concurrent diuretics) - o Impotence/sexual dysfunction - o ↑ urinary frequency → due to prostatic SM relaxation - o Miosis → prevent stimulation of radial fibres of iris

	○ Dry mouth - α_2 antagonist side-effects: ○ Arrhythmias and angina pectoris → due to BRR-mediated ↑ HR and contractility caused by lack of –ve feedback of NAd on own release (may require concurrent β-blockers) ○ ↑ RAAS response ○ ↓ BGL → due to loss of inhibitory effects of Adr on insulin secretion - Others: ○ Hypersensitivity reactions (manifesting as acute bronchospasms, esp in asthmatics) → due to sulphites ○ ↑ GI secretion/motility (AP, diarrhoea, hyperperistalsis) → due to overdominant PNS activity
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Phenoxybenzamine:

- Structure – Haloalkylamine derivative (3° amine)
- Presentation and dosing:
 - Capsule (10 mg) → commenced at PO 10 mg and ↑ daily until BP controlled (usually 1-2 mg/kg/day)
 - Straw-coloured solution for IV (50 mg/mL in HCl form diluted in 200 mL N/S) → 1 mg/kg/day given as slow IVI via CVC
- Clinical uses:
 - (i) Preoperative management of pheochromocytoma (relieves extreme peripheral vasoconstriction → allow expansion of IV compartment)
 - (ii) Treat acute hypertensive crisis
 - (iii) Treat cutaneous vasoconstriction a/w Raynaud syndrome
 - (iv) Adjunct to treat severe shock a/w SNS outflow (I.e. hypovolemia, cardiogenic) → ↓ tissue ischaemia caused by intense peripheral vasoconstriction
- Mechanism of action:
 - Non-selective α blocker (postsynaptic α_1 and presynaptic α_2 receptors) → ↑ affinity for α_1 than α_2 receptors
 - Non-competitive blockade → forms an irreversible covalent bond to α receptor → very long-lasting effects (subsides when drug metabolised only!)

- Pharmacokinetics:

Absorption	- PO (variable GIT absorption with 25% bioavailability) - IV (slow onset with max effect after 1 hr → due to structural modification required to render drug active!)
Distribution	Highly lipophilic
Metabolism/ Elimination	- Hepatic metabolism (via deacetylation) → excreted in urine and bile - Elimination $t_{1/2}$ 24 hrs (but effects last for 72 hrs as new α-receptors need to be regenerated → thus effects compound with repeated dosing!)

- Pharmacodynamic effects:

CVS	Same as phentolamine (see above)
Side-effects	Similar as phentolamine (except it causes contact dermatitis, and does not cause GI or hypersensitivity reactions)

(II) Selective α_1 -adrenoceptor antagonists:

Prazosin:

- Structure – Quinazoline derivative
- Presentation and dosing – Tablets (0.5-5 mg) → 0.5 mg tds (up to 20 mg/day)
- Clinical uses:
 - (i) Treat essential HT
 - (ii) Treat LVF (due to afterload reduction)

- (iii) Relieves vasospasms a/w Raynaud's syndrome
- (iv) Relieves bladder outlet obstruction a/w BPH
- (v) Preoperative management of pheochromocytoma
- Mechanism of action – Competitive selective competitive α_1 receptor antagonist
- Pharmacokinetics:

Absorption	PO only (variable bioavailability (50-80%) due to extensive hepatic first-pass metabolism)
Distribution	Highly protein bound (esp to albumin) – 90%
Metabolism/ Elimination	- Extensive hepatic metabolism (via demethylation/conjugation) → some active metabolites; < 10% excreted unchanged in urine - Elimination $t_{1/2}$ 3 hrs

- Pharmacodynamic effects:

CVS	- ↓ SVR (due to peripheral arteriolar vasodilation) → ↓ BP - ↓ venous return (due to venodilation) → ↓ preload and C.O. - ↓ PVR and PAP (due to pulmonary arteriolar vasodilation) - ↑ coronary blood flow (due to coronary arteriolar dilation) - Venodilation effect >>> arteriolar dilation effect → a/w ↑ postural hypotension - Lack of reflex tachycardia/↑ contractility due to lack of α_2 antagonism (I.e. -ve feedback on NAd release from nerve terminal remains intact → ↓ SNS outflow)
Side-effects	- Orthostatic hypotension and dizziness (leading to syncope, esp on 1st dose; also excessive hypotension during neuraxial block/GA due to ↓ compensatory vasoconstriction and lack of response to α_1 agonists) - CNS symptoms (esp lethargy, drowsiness, headaches, vertigo) - Nasal congestion → due to dilation of nasal mucosal vessels - Fluid retention (needing concurrent diuretics) - Impotence/sexual dysfunction - ↑ urinary frequency → due to prostatic SM relaxation - Miosis → prevent stimulation of radial fibres of iris - Dry mouth

Others (Terazosin, Tamsulosin, Etc.):

- Long-acting oral agents used to treat BPH → relieve α_1 -mediated contraction of prostatic SM
- Similar side-effects to prazosin (esp orthostatic hypotension, vertigo, syncope, Etc.)

(II) **Selective α_2 -adrenoceptor antagonists:**

Yohimbine:

- Uses – Treat impotence, and idiopathic orthostatic hypotension
- Mechanism – Selective competitive α_2 receptor antagonist → ↑ NAd release from nerve endings
- CVS effects – ↑ HR and BP due to ↑ SNS outflow
- Side-effects – Rhinorrhoea, fluid retention, CNS effects as it crosses BBB (anxiety, mania, dissociative states, paraesthesia, tremor)

β-Adrenoceptor Antagonists:

“β-adrenoceptor antagonists”:

- Bind selectively to β-adrenergic receptors (either β₁, or both β₁ and β₂) → prevent catecholamines or other sympathomimetics from provoking a β response
- All are competitive antagonists
- Note – Propranolol is the “standard” drug that all β-blockers are compared to

Remember – β-adrenoceptor response (all postsynaptic):

- β₁ (GPCR; G_s) – +ve inotropic, dromotropic, and chronotropic cardiac effects, renin release (from JGA), and GI SM relaxation
- β₂ (GPCR; G_s) – Peripheral vasodilation, bronchodilation, GI and uterine SM relaxation, muscle tremors, and hepatic glycogenolysis
- β₃ (GPCR; G_s) – Lipolysis (esp brown fat)

(I) Classification of β-adrenoceptor antagonists:

- (1) Receptor selectivity
 - o (i) Cardioselective (β₁ selective) – Eg. atenolol, esmolol, metoprolol
 - Produces desired cardiac effects (-ve inotropy, chronotropy, dromotropy) with less unwanted β₂ antagonist effects (bronchoconstriction, peripheral vasoconstriction, hypoglycaemia) → safer to use in pts with obstructive AW diseases, PVD or DM
 - Note: Selectivity is dose-dependent → at high doses, β₁ selectivity is lost!
 - o (ii) Non-selective (both β₁ and β₂) – Eg. propranolol
 - Associated with unwanted β₂ antagonist effects (see above)
- (2) Intrinsic sympathomimetic activity
 - o (i) Possess intrinsic sympathomimetic activity (partial agonist) – Eg. pindolol, timolol, acetbutolol, labetalol
 - Produce sympathomimetic effects when SNS tone and circulating levels of catecholamine are ↓, but produce antagonist effects when they are ↑
 - Less likely to cause bradycardia and HF in pts with mild LVF (but should be avoided in those with severe LVF as it further ↓ C.O.)
 - o (ii) Lacking intrinsic sympathomimetic activity (pure antagonist) – other β-blockers
 - Produce antagonist effects regardless of SNS tone/circulating [catecholamines]
- (3) Cardiac membrane stabilising activity
 - o (i) Possess cardiac membrane stabilising activity (Eg. metoprolol, propranolol, labetalol, acetabulol, timolol, pindolol) → lacks clinical significance as such activity manifests only at doses higher than required to produce clinically relevant β-blockade
 - o (ii) Lacks cardiac membrane stabilising activity (other β-blockers)

(II) Pharmacodynamic effects of β-adrenoreceptor antagonists:

Note – Effects of β-blocker will vary depending on its (i) receptor selectivity and (ii) intrinsic sympathomimetic activity

Cardiac	- -ve inotropic effect (β₁) → ↓ contractility - -ve chronotropic effect (β₁) → ↓ HR due to ↓ SAN automaticity (↓ phase 4 spontaneous depolarisation rate) and ↓ AVN conduction rate - Antiarrhythmic effect (β₁) → suppresses effects of SNS/catecholamine activity - Favours myocardial O₂ supply > demand (β₁) → relieves myocardial ischaemia - o Generally ↑ O₂ supply (due to ↑ diastolic perfusion time of coronary arteries due to ↓ HR) and ↓ O₂ demand (due to ↓ HR/contractility) - o But can ↓ O₂ supply (due to coronary vasoconstriction 2° to β₂)
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	antagonism) and $\uparrow$ O_2 demand (due to ventricular dilation and prolonged systolic ejection) Note – These effects are more pronounced with $\uparrow$ SNS activity (I.e. during activity or HR; cf. at rest)
Vascular	- $\downarrow$ BP due to: - o $\downarrow$ C.O. a/w $\downarrow$ HR/contractility (cardiac β_1) - o $\downarrow$ renin release (β_1 at JGA) $\rightarrow$ $\downarrow$ AII and aldosterone production - o Blunts response of BRR - o Central effect - Vasoconstriction of coronary and peripheral vessels (vascular β_2) - o Peripheral vasoconstriction $\rightarrow$ mild HTN, poor peripheral circulation (I.e. cold hands/feet), accentuates vasospasms a/w Raynaud's disease $\rightarrow$ issue with underlying PVD or if there is unopposed α-induced vasoconstriction (I.e. phenylephrine, clonidine) due to risk of paradoxical HTN - o Coronary vasoconstriction $\rightarrow$ $\downarrow$ coronary blood flow
Respiratory	Bronchospasm (β_2) $\rightarrow$ issue with underlying obstructive AW disease
CNS	Depression, hallucinations/paranoia, nightmares, fatigue/lethargy, memory loss $\rightarrow$ generally occurs with lipid-soluble β -blockers (esp propranolol, metoprolol)
Ocular	$\downarrow$ IOP ($\downarrow$ aqueous humour production)
GI	Dry mouth and GI disturbances (N/V and diarrhoea) (β_2)
Metabolic	- $\downarrow$ BGL due to $\downarrow$ hepatic glycogenolysis (β_2) and masks symptoms of hypoglycaemia (esp tachycardia; β_1) $\rightarrow$ avoid using non-selective β-blockers in DM pts on insulin or hypoglycaemics - $\uparrow$ TG but $\downarrow$ FFA due to $\downarrow$ lipolysis (β_2) - $\uparrow$ K^+ due to $\downarrow$ IC shift into skeletal muscle (β_2)
Obstetrics, foetal and newborn	- Lipid-soluble β-blockers cross placenta and breast milk $\rightarrow$ causes bradycardia, hypotension and hypoglycaemia in foetus and newborn - Uterine contraction (β_2)
Other side-effects	Fever, rash, alopecia, thrombocytopenia, myopathy
Withdrawal syndrome	- Acute cessation of chronic β-blocker therapy $\rightarrow$ excess SNS activity within 24-48 hrs of cessation (risk of rebound HTN, myocardial ischaemia, arrhythmias) - Mechanism – Chronic β-blocker therapy $\rightarrow$ upregulation of β-receptor #'s - Prevention – Infuse propranolol continuously in those who cannot take oral β-blockers during peri-operative period
Drug interactions	- Additive myocardial depression with IV induction agents and volatiles (enflurane $>$ sevoflurane/desflurane $>$ isoflurane) - $\downarrow$ efficacy of endogenous inotropes and vasopressors - β-blockers unmask direct -ve inotropy of drugs that $\uparrow$ SNS activity (Eg. ketamine) $\rightarrow$ $\downarrow$ C.O. and BP

Aside: β -blocker toxicity

- Features – Mainly myocardial depression (bradycardia, $\downarrow$ C.O., hypotension, cardiogenic shock), but also bronchospasm and $\downarrow$ ventilation, seizures and prolonged intraventricular conduction of cardiac impulses (due to LA-nature of some agents), and rarely hypoglycaemia
- Management of myocardial depression:
 - o (i) Atropine $\rightarrow$ block vagal effect on heart and unmask any residual SNS activity
 - o (ii) β agonists to overcome effect of competitive β -blockade:
 - Isoprenaline (non-selective β agonist) $\rightarrow$ causes vasodilation (β_2) prior to +ve inotropy (β_1)
 - Dobutamine (β_1 agonist) $\rightarrow$ causes α -induced vasoconstriction with the high-doses required to overcome β -blockade (and thus not recommended)
 - o (iii) Glucagon $\rightarrow$ acts independent of β -receptor blockade by stimulating Gs ($\uparrow$ IC cAMP)
 - o (iv) CaCl $\rightarrow$ acts independent of β -receptor blockade
 - o (v) Consider transvenous artificial cardiac pacemaker or HDx (if β -blocker minimally protein bound) in situations refractory to drug therapy

(III) Pharmacokinetics of β -adrenoreceptor antagonists:

- Main differences b/t β -blockers is their lipid solubility:
 - o $\downarrow$ solubility (Ie. atenolol) $\rightarrow$ poor GI absorption, does not cross BBB, placenta or breast milk, minimal hepatic metabolism (excreted unchanged in urine) and protein binding, and longer elimination $t_{1/2}$
 - o $\uparrow$ solubility (Ie. propranolol) $\rightarrow$ opposite effects
- For individual agent pharmacokinetics $\rightarrow$ see tables below

(IV) Clinical uses of β -adrenoreceptor antagonists:

- (1) Treatment of essential HTN (Eg. propranolol, atenolol, metoprolol, carvedilol)
 - o $\downarrow$ BP due to (i) $\downarrow$ CO 2° to $\downarrow$ HR (but also $\downarrow$ contractility at higher doses), and (ii) also antagonism of RAAS activity (via β_1 effect)
 - o Not associated with orthostatic hypotension
 - o Generally used with vasodilator drug (minimises reflex $\uparrow$ HR/contractility a/w BRR response, and fluid overload a/w RAAS activation)
- (2) Treatment of angina pectoris (Eg. propranolol, metoprolol, atenolol)
 - o $\downarrow$ myocardial ischaemia by favouring myocardial O_2 supply $>$ O_2 demand (see above)
- (3) Treatment of peri-MI/prophylaxis post-MI (propranolol, atenolol, metoprolol)
 - o $\downarrow$ incidence of reinfarction, recurrent ischaemia, and catecholamine-induced arrhythmias a/w sudden cardiac death
- (4) Management of CHF (Eg. metoprolol, carvedilol) $\rightarrow \uparrow$ LVEF and improves survival
- (5) Manage conditions a/w $\uparrow$ levels of catecholamines:
 - o (i) Pheochromocytoma (prevent reflex tachycardia a/w α -blockade)
 - o (ii) Hyperthyroidism (propranolol is better than metoprolol or esmolol as it suppresses $T_4 \rightarrow T_3$ conversion peripherally)
 - o (iii) HOCM and cyanotic spells of TOF
 - o (iv) Anxiety (Eg. propranolol)
 - o (v) Blunt BRR-mediated by vasodilators
 - o (vi) Suppress intra-operative response to noxious stimuli (Eg. laryngoscopy, extubation, surgery) (Eg. esmolol)
- (6) Antiarrhythmic agents (class II) $\rightarrow$ all β -blockers can be used to treat arrhythmias (AF/flutter, torsades de pointes) a/w $\uparrow$ levels of catecholamines (Ie. perioperative stress, TTX, pheochromocytoma)
- (7) Treatment of essential tremor (Eg. propranolol)
- (8) Prophylaxis of migraine (Eg. propranolol, metoprolol)
- (9) Perioperative beta-blockade (Eg. atenolol, metoprolol, esmolol)
 - o Given to pts at risk of myocardial ischaemia (CAD, +ve stress test, IDDM, LVH) during high risk surgery (vascular, thoracic, intraperitoneal surgery or surgery with expected large blood loss) $\rightarrow$ aim HR $\sim$ 65-80 bpm
 - o Mechanism of $\downarrow$ perioperative risk of myocardial ischaemia – $\downarrow$ cardiac MRO_2 (esp in ischaemic myocardium) due to $\downarrow$ HR/contractility, attenuates effects of endogenous catecholamines, $\uparrow$ coronary blood flow due to $\uparrow$ diastolic time (esp redistributes coronary blood flow to ischaemic areas), plaque stabilisation (due to $\downarrow$ shear forces), and antiarrhythmic effect
- (10) Treat intra-operative myocardial ischaemia (Eg. esmolol, atenolol, propranolol) $\rightarrow \downarrow$ HR to 60 bpm to attenuate further ischaemia

Important to note $\rightarrow$ β -blockers should be continued throughout peri-operative period to (i) maintain drug effect (Ie. anti-HTN) and (ii) avoid the withdrawal syndrome

Important to note:

- Absolute contraindication – (i) unstable LVF (ppt acute HF), (ii) severe bradycardia (ppt sinus arrest), or (iii) preexisting AV heart block (ppt complete HB)
- Relative contraindications – (i) obstructive AW disease (esp non-selective or high dose β_1 selective), (ii) PVD (esp non-selective or high dose β_1 selective), (iii) hypovolaemia with compensatory tachycardia (risk profound hypotension), and (iv) mental depression
- Caution in DM patients → risk of hypoglycaemia (non-selective agents) and masking of hypoglycaemic symptoms (esp tachycardia)

(V) Overview of individual β -adrenoreceptor antagonists:

Propranolol:

- Clinical uses:
 - o Several – Treat HTN, AP, peri/post-MI, hyperthyroidism, essential tremor, anxiety, intraoperative myocardial ischaemia, anti-arrhythmic, migraine prevention
 - o “Standard” drug that all β -blockers are compared to
- Preparation and dosing – 10-160 mg tablets → PO 160-320 mg/day; clear colourless solution (1 mg/mL) → IV 0.5 mg every 5 mins, titrated up to 10 mg
- Mechanism of action:
 - o Competitive non-selective β -adrenoceptor antagonist (β_1 and β_2 effects equal) with cardiac membrane-stabilising activity. Lacks intrinsic sympathomimetic activity
 - o Racemic mixture → S-isomer (most β -blocker effects); R-isomer (prevent peripheral T₄→T₃ conversion)
- Pharmacokinetics:

Absorption	- PO (well-absorbed in GIT (90%) but extensive hepatic first-pass metabolism (30% bioavailability) → thus, requires very high oral dosages!) - IV
Distribution	- ↑ lipid soluble (+++) → ↑ CNS/placenta/breast milk transfer - ↑ protein binding (90-95%) to α_1 -acid glycoprotein - V _D 3.6 L/kg
Metabolism/ Elimination	- Hepatic metabolism to an active metabolite (4-HO-propranolol) that is equally active but shorter elimination t _{1/2} than parent compound - Elimination t _{1/2} 4 hrs (↑ rapid metabolism of R-isomer cf. S-isomer) - Nb. Liver failure (↓ HBF and/or enzyme activity) → ↓ clearance of drug; renal failure → ↓ clearance of active metabolite
- Drug interactions:
 - o Heparin – ↑ free level of propranolol due to ↓ protein binding (as heparin ↑ FFA (due to ↑ LPL activity), which displaces propranolol from proteins)
 - o Fentanyl – Propranolol significantly ↓ pulmonary first-pass uptake of fentanyl (as they are both basic lipophilic amines taken up by lungs)
 - o Amide LA – Propranolol ↓ their hepatic clearance (due to ↓ HBF and enzyme activity)

Esmolol:

- Clinical uses:
 - o Rapid onset and offset → effect within 5 mins, and lasts up to 10-30 mins
 - o Perioperative β -blockade in pts at high risk for CAD in non-cardiac surgery
 - o Intra-operative management of ↑ HR and BP a/w SNS-response induced by noxious stimuli (surgery or intubation), hyperthyroidism, phaeochromocytoma, HOCM or TOF cyanotic spells
 - o Manage acute intra-operative SVTs (AF/flutter) and myocardial ischaemia
 - o Manage PIH intraoperatively
- Preparation and dosing – Clear colourless solution at pH 4.5-5.5 (either 2.5 g or 100 mg in 10 mL) – Former diluted and IVI at 50-200 ug/kg/min; latter given as IV 10 mg boluses titrated to effect

- Mechanism of action – Competitive β_1 -selective adrenoceptor antagonist without intrinsic sympathomimetic activity and cardiac membrane stabilising properties
- Pharmacokinetics:

Absorption	IV only
Distribution	- $\uparrow$ lipid soluble (+++) $\rightarrow \uparrow$ CNS/placenta/breast milk transfer - 60% protein-bound - V_D 3.5 L/kg
Metabolism/ Elimination	- Rapid organ-independent metabolism by RBC esterases (via hydrolysis) into an inactive acid metabolite and methanol - Elimination $t_{1/2}$ 10 mins only! - Nb. Does NOT affect metabolism of SCh (which is metabolised by plasma cholinesterase)

- Issues with use:
 - o Very short-lived effects (due to short elimination $t_{1/2}$)
 - o Irritant to veins $\rightarrow$ extravasation causes tissue necrosis (due to $\downarrow$ pH)
 - o Unmasks β_2 -mediated vasodilation a/w Adr-secreting tumour
 - o Risk of APO and CVS collapse when treating Adr/cocaine-induced CVS toxicity (due to removal of compensatory $\uparrow$ HR/contractility for catecholamine-mediated-
 $\uparrow$ LV afterload) $\rightarrow$ use vasodilator drugs (SNP/GTN) instead

Atenolol:

- Clinical uses – Perioperative β -blockade in pts at high risk for CAD in non-cardiac surgery, treat HTN, angina pectoris, peri/post-MI, anti-arrhythmic
- Mechanism of action – Competitive β_1 -selective adrenoceptor antagonist without intrinsic sympathomimetic activity and cardiac membrane stabilising properties
- Preparation and dosing – 25-100 mg tablets and 5 mg/mL syrup $\rightarrow$ PO 50-100 mg/day; clear colourless solution (0.5 mg/mL) $\rightarrow$ IV 2.5 mg (repeated up to 10 mg), then an infusion titrated to effect
- Pharmacokinetics:

Absorption	- PO (incomplete GI absorption (45%) with 45% bioavailability) - IV only
Distribution	- $\downarrow$ lipid soluble (+) $\rightarrow \downarrow$ CNS/placenta/breast milk transfer - 5% protein-bound - V_D 0.7 L/kg
Metabolism/ Elimination	- Renally cleared (no hepatic metabolism) - Elimination $t_{1/2}$ 7 hrs (prolonged with renal failure)

Metoprolol:

- Clinical uses – Perioperative β -blockade in pts at high risk for CAD in non-cardiac surgery, treat HTN, angina pectoris, peri/post-MI, anti-arrhythmic, hyperthyroidism (but lacking T4 $\rightarrow$ T3 inhibition), and migraine prophylaxis
- Preparation and dosing – Tablets (25-100 mg) $\rightarrow$ PO 50-200 mg daily; Clear and colourless solution (1 mg/mL) $\rightarrow$ up to 5 mg IV
- Mechanism of action – Competitive β_1 -selective adrenoceptor antagonist with cardiac membrane stabilising properties (but without intrinsic sympathomimetic activity)
- Pharmacokinetics:

Absorption	- PO (rapid GI absorption (95%) with high hepatic first-pass metabolism (50% bioavailability) - IV
Distribution	- $\uparrow$ lipid soluble (+++) $\rightarrow \uparrow$ CNS/placenta/breast milk transfer - Low (20%) protein-binding
Metabolism/ Elimination	- Hepatic metabolism into inactive metabolites - Variable elimination $t_{1/2}$ 3-7 hrs (depending on slow vs fast hydroxylators)

Carvedilol:

- Clinical uses – Mild-moderate CHF due to myocardial ischaemia/cardiomyopathy, and treat HTN

- Mechanism of action – Competitive non-selective β and α_1 antagonist, without intrinsic sympathomimetic activity and cardiac membrane stabilising properties
- Pharmacokinetics – Given PO only. Extensive protein binding and hepatic metabolism to weakly active metabolites. Elimination $t_{1/2}$ 7-10 hrs

Sotalol:

- Clinical uses – Antiarrhythmic (treat VT and atrial tachyarrhythmias, prevent PSVT) → NOT used for angina pectoris, peri/post-MI, HTN or any other situations
- Preparation and dosing – Tablets (PO 80-160 mg bd); Clear colourless solution (IV 50-100 mg)
- Mechanism of action:
 - o Non-selective β -adrenergic antagonist (class II) → at low doses
 - o Class I (Na^+ blockade) and class III (K^+ channel blocker) effects at higher doses
 - o Exists as a racemic mixture (L isomer → β -adrenergic antagonist and class III effect; D-isomer → class III effect and ↑ mortality in those with LVF/recent MI)
- Pharmacokinetics:

Absorption	PO (well absorbed in GIT (85%) with 90% bioavailability) and IV
Distribution	No plasma protein binding; lipid solubility (+)
Metabolism/ Elimination	Not metabolised → excreted unchanged (90% in urine; 10% in bile) Elimination $t_{1/2}$ 15 hrs Nb. clearance largely impacted by renal failure
- Issues – Torsades de Pointes 2° to prolonged QTc (esp with large doses, renal failure, underlying prolonged QTc, electrolyte imbalance ($\downarrow \text{K}^+ / \downarrow \text{Mg}^{2+}$))

Combined α - and β -Adrenoceptor Antagonists:

Labetalol:

Structure of labetalol:

- Synthetic salicylamide derivative with 2 asymmetric centres $\rightarrow$ 4 stereoisomers in equal proportions:
 - o SR-isomer $\rightarrow$ selective α_1 antagonism
 - o RR-isomer $\rightarrow$ non-selective β effect antagonism

Presentations of labetalol:

- Tablets (50-400 mg)
- Clear colourless solution for IV in HCl formulation (5 mg/mL)

Clinical uses of labetalol:

- (1) Treat acute hypertensive crises (esp due to phaeochromocytoma, clonidine withdrawal, Adr overdose) $\rightarrow$ IV 5-20 mg titrated up to 200 mg max (with effect within 5-10 mins)
- (2) Controlled hypotension for use in anaesthesia $\rightarrow$ given IV as above
- (3) Blunt reflex tachycardia/hypertensive response 2 $^\circ$ to intubation/surgical stimuli in anaesthetised patients $\rightarrow$ given IV as above
- (4) Treat HTN (esp a/w angina) $\rightarrow$ PO 100-800 mg bd (up to 2.4 mg daily)

Mechanism of action of labetalol:

- Has both effects:
 - o Selective α_1 -antagonism $\rightarrow$ causes $\downarrow$ SVR (due to peripheral vasodilation) $\rightarrow$ $\downarrow$ BP
 - o Non-selective β antagonism $\rightarrow$ prevents reflex tachycardia/ $\uparrow$ contractility triggered by BRR in response to $\downarrow$ BP
- α_1 : β antagonism dependent on route $\rightarrow$ 1:3 PO; 1:7 IV

Pharmacokinetics of labetalol:

Absorption	- PO (well-absorbed from GIT (70%)) but extensive hepatic first-pass metabolism $\rightarrow$ bioavailability 25%. This $\uparrow$ with food ingestion and $\uparrow$ age! - IV
Distribution	Highly lipid soluble (+++); 50% bound to plasma protein
Metabolism/ Elimination	- Extensive hepatic metabolism (conjugated to glucuronide into several inactive metabolites) with only 5% excreted unchanged in urine - Elimination $t_{1/2}$ 5-8 hrs

Pharmacodynamic effects of labetalol:

CVS	- $\downarrow$ BP due to $\downarrow$ SVR (α_1 antagonism) - C.O. unchanged due to blunting of reflex $\uparrow$ HR and contractility due to BRR (β antagonism) - $\downarrow$ myocardial MRO ₂ due to $\downarrow$ afterload and blunting of $\uparrow$ HR/+ve inotropy due to BRR
Side-effects	- Mainly side-effects of α_1 antagonism $\rightarrow$ 1 $^\circ$ ly orthostatic hypotension, fluid retention, dry mouth, nasal congestion, urinary frequency, sexual dysfunction - Side-effects of β antagonism less common $\rightarrow$ bronchospasms, LVF, bradycardia, heart block, nightmares, cramps, Etc. - Chronic oral therapy $\rightarrow$ fluid retention (needs diuretic therapy)

ANTI-ARRHYTHMIC DRUGS

- (a) *To classify antiarrhythmic agents by their electro-physiological activity and mechanisms of action.*

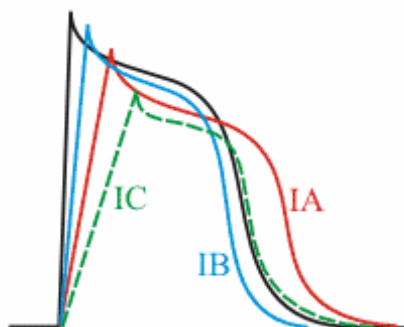
Vaughan-Williams classification:

Class		Mechanism	Example
I	a	Inhibit fast Na ⁺ channels (moderate potency)	Quinidine, procainamide, disopyramide
	b	Inhibit fast Na ⁺ channels (mild potency)	Lignocaine, phenytoin, mexiletine
	c	Inhibit fast Na ⁺ channels (most potent)	Flecainide, propafenone
II		β-adrenergic antagonists	Propranolol, atenolol, esmolol, metoprolol
III		K ⁺ channel blockers	Amiodarone, sotalol, ibutilide, bretylium
IV		Slow-type (L-type) VG Ca ²⁺ channel blockers	Verapamil, diltiazem
Others		Digoxin, Adenosine, Magnesium	

(b) *To describe the pharmacology of the sodium channel blocking agents with particular reference to lignocaine and flecainide.*

Overview of Class I agents:

- Mechanism – Inhibit fast Na^+ channels during phase 0 (depolarisation) of cardiac AP → ↓ depolarisation rate and conduction velocity
- Subtypes:
 - o Class IA (quinidine, procainamide, disopyramide)
 - Moderate potent fast Na^+ channel inhibition → moderate ↓ depolarisation rate and conduction velocity
 - Lengthens cardiac AP duration and effective refractory period
 - o Class IB (lignocaine, phenytoin, mexiletine)
 - Least potent fast Na^+ channel inhibition → minimal ↓ depolarisation rate and conduction velocity
 - Shortens cardiac AP duration and effective refractory period
 - o Class IC (flecainide, propafenone)
 - Most potent fast Na^+ channel inhibition → significant ↓ depolarisation rate and conduction velocity
 - No effect on cardiac AP duration and effective refractory period



Lignocaine:

Type: Class IB agent – Amide LA agent

Antiarrhythmic effects:

- Treat sustained VT and PVBs → esp when a/w myocardial ischaemia (due to more inactivated Na^+ channels present) or re-entry

Mechanism of action:

- Class IB effect – (i) Least potent fast Na^+ channel inhibition → minimal ↓ depolarisation rate (phase 0) and conduction velocity, and (ii) Shortens cardiac AP duration and effective refractory period

Pharmacokinetics:

Absorption	IV only (as significant hepatic first-pass metabolism when given PO)
Distribution	70% protein bound
Metabolism/ Elimination	- Hepatic metabolism → forms active metabolite (has anti-arrhythmic effects) → then excreted in urine - Elimination $t_{1/2}$ 90 mins → ↑ with decreased HBF (Eg. CCF, hepatic failure)

Side-effects:

- Aim therapeutic plasma level 1-5 ug/mL
- CNS toxicity occur at plasma level 5-10 ug/mL:

- Excitatory symptoms initially → circumoral tingling, dizziness, tinnitus, paraesthesia, irritation/agitation, then seizures
- Depressive symptoms later → CNS depression, confusion, apnoea, coma
- CVS toxicity occur at plasma level > 10 ug/mL
 - Bradycardia and AV heart block
 - Unresponsive hypotension due to -ve inotropic effects and peripheral vasodilation

Flecainide:

Type: Class IC agent – Fluorinated amide LA analogue of procainamide

Antiarrhythmic effects:

- Uses: VPBs and VT and atrial tachyarrhythmias, SVT a/w WPW (as it delays conduction of accessory bypass tracts)

Mechanism of action:

- Class IC effect – (i) Most potent fast Na⁺ channel inhibition → significant ↓ depolarisation rate (phase 0) and conduction velocity, (ii) No effect on cardiac AP duration and effective refractory period

Pharmacokinetics:

Absorption	PO (90% bioavailability) and IV
Distribution	50% plasma protein bound
Metabolism/ Elimination	Hepatic metabolism into weak active metabolites → excreted in urine Also excreted in urine unchanged Prolonged elimination t _{1/2} 20 hrs → prolonged with renal and cardiac failure

Side-effects:

- (i) Very pro-dysrhythmic → esp with LVF, underlying conduction disorders, and post-MI
 - Prolongs QRS and PR interval → AV or infranodal conduction block (thus contraindicated in those with 2nd/3rd degree AV heart blocks)
 - Depress SAN function → sinus arrest
 - NOT to be given post-MI → very high risk of sudden cardiac death
 - Raises pacing threshold
- (ii) Precipitate heart failure 2° to moderate -ve inotropic effect
- (iii) Others: vertigo/dizziness, headaches, paraesthesia, difficulty with visual accommodation

(c) ***To describe the pharmacology of the beta-blockers with reference to their antiarrhythmic properties.***

β-blockers used as anti-arrhythmics:

- Non-selective – Propranolol, Sotalol
- β₁-selective – Esmolol, Metoprolol, Atenolol

Antiarrhythmic effects:

- Used to treat arrhythmias related to ↑ SNS activity and circulating catecholamines (I.e. perioperative stress, TTX, pheochromocytoma, CCF, Etc.) → includes:
 - o (i) Sinus tachycardia
 - o (ii) Rate control of AF/atrial flutter
 - o (iii) Treat multifocal atrial tachycardia
 - o (iv) Treat frequent VEBs
 - o (v) Control Torsades de Pointes in patients with prolonged QTc
 - o (vi) Prevent sudden cardiac death following MI and peri-operatively

Mechanism of action:

- Mainly via class II effect (block β₁ receptors of heart) → blunt effect of SNS stimulation and circulating catecholamines → ↓ rate of spontaneous phase 4 depolarisation → results in ↓ SAN activity (-ve chronotropy) and AVN activity (slowed AVN conduction rate)
- Also stabilises membrane electrical activity (class I effect); Sotalol has class III (K⁺ channel blocking) effect
- Depress myocardium (via direct effect and β₁ effect)

Pharmacokinetics:

- Propranolol – Given PO or IV. Extensive hepatic 1st-pass metabolism (4-HO-propranolol is a weak active metabolite. Elimination t_{1/2} 2-4 hrs (although has 6-8 hrs of effect)
- Sotalol – See below
- Metoprolol and Esmolol – See “Adrenergic pharmacology”

Side-effects:

- (i) CVS:
 - o Bradycardia, HB and even systolic arrest (esp in those with AV heart block or taking other SAN/AVN blocking agents (Eg. lignocaine, CCB))
 - o Hypotension
 - o Myocardial depression → leads to HF (esp in those with LVF)
- (ii) Respiratory → bronchospasm (esp if underlying asthma/COPD)
- (iii) CNS → fatigue and depression
- (iv) Endocrine → masks hypoglycaemic symptoms
- (v) GI → ↑ reflux, N/V
- (vi) Others: Drug fever, allergic rash, cold extremities and worsening of Raynaud's

Important to note → β-receptors upregulate with chronic β-blocker use → thus avoid abrupt cessation of drug to prevent rebound HTN/tachyarrhythmias

(d) ***To describe the pharmacology of the potassium channel blockers with particular reference to amiodarone, sotalol and ibutilide.***

(I) Amiodarone:

Structure: Iodinated benzofurane derivative (resembles thyroxine)

Antiarrhythmic effects:

- (i) Treat SVT (including SVT a/w WPW → depresses both AVN and accessory pathway conduction)
- (ii) Treat VT
- (iii) Treat atrial tachyarrhythmias (including AF/atrial flutter)

Aside – Dosing:

- IV: Loading dose 5 mg/kg over 1 hr → then 15 mg/kg infusion over 24 hrs
- PO: 200 mg tds 1 week → then 200 mg bd for 1 week → then 200 mg daily thereafter

Mechanism of action:

- (i) Mainly a class III anti-arrhythmic effect → blocks K^+ channel → has following effects in all cardiac tissues (even accessory bypass tract):
 - Prolongs cardiac depolarisation
 - Slows rate of repolarisation → prolongs effective refractory period
 - Increases duration of AP
- (ii) Also has class I (Na^+ blockade), class II (β -blockade) and class IV (CCB) effect
- (iii) Antiadrenergic effect → non-competitive inhibition of α and β receptors

Pharmacokinetics:

Absorption	PO (poorly absorbed from gut; 50-70% bioavailability) or IV (must be diluted in D5W)
Distribution	- Extensive protein binding (95%) - Large V_D (up to 70 L/kg) → stored avidly in tissues (esp muscle and fat)
Metabolism/ Elimination	- Hepatic metabolism → produces an active metabolite (desmethyramiodarone) that has a longer elimination $t_{1/2}$ than parent drug → accumulates with chronic therapy - Very long elimination $t_{1/2}$ (20-100 days) → this means after cessation, effects (including S/E) persist up to 60 days!!! - Excreted in bile and faeces, and also via skin and lacrimal glands (minimally via urine)

Side-effects:

Note:

- Side-effects generally occur with chronic treatment with daily dosage > 400 mg
- Most side-effects are reversible, especially if ceased early

Respiratory	- Includes – Pulmonary alveolitis/pneumonitis (most serious), fibrosis, pleuritis, APO/ARDS (esp post-operatively after cardiopulmonary bypass) - 2 presentation: - (i) Slow insidious onset of progressive dyspnoea, cough, pulmonary infiltrates on CXR (more common) - (ii) Acute onset of dyspnoea, cough ↓ PaO_2 and fever (mimics infectious pneumonia) → includes post-operative APO
CVS	- Mechanism – Oxidative cellular damage 2° to ↑ free O_2 radicals → accelerated in presence of ↑ FIO_2 (thus limit FIO_2 in pts receiving amiodarone) - Incidence of 5-15% with 5-10% mortality
	- Risk of Torsades de Pointes (polymorphic VT) 2° to prolonged QTc → esp in presence of preexisting prolonged QTc (congenital or due to drugs (Eg. TCA)) - Bradycardia, AV heart block and even sinus arrest (esp with drugs that depress SAN (Eg. lignocaine) or AVN (Eg. CCB, β -blocker)) → resistant to atropine → thus,

	amiodarone is contraindicated with SSS or HB - ↓ C.O. 2° to mild direct –ve inotropy → exacerbated with other –ve inotropic drugs (Eg. GA, CCB, β-blockers) - Hypotension 2° to peripheral vasodilation (due to antiadrenergic effects) - ↓ responsiveness to catecholamines (Eg. NAd, Adr) and SNS stimulation (due to antiadrenergic effects)
CNS	- Peripheral neuropathy - Tremors - Sleep disturbances - Headaches - Proximal skeletal muscle weakness
Endocrine	Hypo- and hyperthyroidism (incidence 2-4%; especially if there is underlying thyroid disease), prevents peripheral conversion of T3 → T4
Eyes	Corneal microdeposits a/w mild visual blurring
Skin	- Photosensitivity, rash, cyanotic discolouration (slate-gray pigmentation) of face - Irritant in peripheral veins (use CVC for IVI)
GI	- Fatty liver, cirrhosis, hepatitis - Dose-dependent LFT derangements
Drug interactions	- Inhibits hepatic CYP450 metabolism of other drugs (Eg. digoxin, warfarin, phenytoin, cyclosporine, Etc.) - Displaces drugs from plasma protein (Eg. digoxin, warfarin, phenytoin)

(II) Sotalol:

Exists as a racemic mixture:

- L isomer → β-adrenergic antagonist and class III effect
- D-isomer → class III effect and ↑ mortality in those with LVF/recent MI

Antiarrhythmic effects:

- (i) Treat sustained VT
- (ii) Prevent PSVT
- (iii) Treat atrial tachyarrhythmia (AF/atrial flutter) → β-blocker effect maintains SR following cardioversion, and maintains ventricular rate with reversion back to AF

Mechanism of action:

- Non-selective β-adrenergic antagonist (class II) → at low doses
- Class I (Na⁺ blockade) and class III (K⁺ channel blocker) effects at higher doses → prolongs cardiac depolarisation, AP duration and effective refractory period in conducting tissues of atria, ventricles, and accessory bypass tracts

Pharmacokinetics:

Absorption	PO (well absorbed with 90% bioavailability) and IV
Distribution	No plasma protein binding
Metabolism/ Elimination	No metabolised → excreted unchanged (90% in urine; 10% in bile) Nb. clearance largely impacted by renal failure

Side-effects:

- (i) Torsades de Pointes 2° to prolonged QTc (esp with large doses, renal failure, underlying prolonged QTc, electrolyte imbalance (↓K⁺/↓Mg²⁺))
- (ii) Issues a/w β-blockade → precipitate heart failure (esp in those with LVF 2° to –ve inotropy), bradycardia and delayed AVN conduction, bronchospasm (esp with asthma), mask symptoms of hypoglycaemia
- (iii) Others: Fatigue, dyspnoea, vertigo, nausea, visual disturbances, sexual dysfunction

(III) Ibutilide:

<i>Antiarrhythmic effects:</i>	Convert recent onset AF/atrial flutter to sinus rhythm
<i>Mechanism of action:</i>	Class III anti-arrhythmic effect → blocks K^+ channel → prolongs cardiac depolarisation, AP duration, and effective refractory period
<i>Pharmacokinetics:</i>	Extensive hepatic metabolism (mainly to inactive metabolites (except for a HO-metabolite that has weak antiarrhythmic effect)
<i>Side-effects:</i>	Torsades de Pointes can occur even WITHOUT QTc prolongation (esp with underlying LVF, prolonged QTc, electrolyte imbalance ($\downarrow K^+ / \downarrow Mg^{2+}$))

(e) ***To describe the pharmacology of the calcium antagonists with reference to their antiarrhythmic properties.***

Calcium channel blockers (CCBs) used as anti-arrhythmics:

- Verapamil (class I – phenylalkylamine)
- Diltiazem (class III – benzothiazepine)

Antiarrhythmic effects:

- (i) Terminate PSVT
- (ii) Rate (and rhythm) control of AF/atrial flutter

Mechanism of action:

- Competitive antagonist of slow inward Ca^{2+} current at L-type VG Ca^{2+} channels → located:
 - o (i) Cardiac pacemaker cells at SAN/AVN → ↓ rate of spontaneous phase 4 depolarisation (↓ automaticity) → ↓ conduction rate through AVN and –ve chronotropy at SAN
 - o (ii) Cardiac contractile cells (less effect) → ↓ Ca^{2+} influx during phase 2 (plateau) → -ve inotropic effect
 - o (iii) Vascular SM cell → relaxation causing vasodilation of coronary and systemic arteries

Pharmacokinetics:

Absorption	PO (90% absorbed but ↑ hepatic 1 st pass metabolism → 25% bioavailability) and IV
Distribution	Highly protein bound in plasma (90%)
Metabolism/ Elimination	- Metabolised by liver into inactive metabolites (although verapamil has an active metabolite – Norverapamil) → then excreted in urine and bile - Elimination $t_{1/2}$ 3-7 hrs

Side-effects:

- (i) Serious bradyarrhythmia and AV heart block → esp if underlying conduction defect or concurrent drugs that slow AV conduction (Eg. digoxin, β -blockers)
- (ii) Precipitate heart failure (esp if underlying LVF or concurrent use of –ve inotropic drugs (Eg. GA, β -blockers)) → CCBs ↓ C.O. 2^o to its direct –ve inotropy
- (iii) Hypotension → due to peripheral vasodilation and ↓ C.O.
- (iv) Precipitate VT if used to treat SVT with underlying WPW → CCBs do not depress accessory tracts; in fact, they induce reflex SNS activity that ↑ conduction across these tracts and ↑ ventricular rate!
- (v) ↑ CBF → due to cerebral artery vasodilation
- (vi) ↑ plasma [] of digoxin
- (vii) Potentiates effects of ND NMBD

(f) **To describe the pharmacology of digoxin with reference to its antiarrhythmic properties.**

Overview of digoxin:

- Digoxin is a cardiac glycoside extracted from the leaves of foxglove plant
- Structure – steroid cyclopentenophenanthrene nucleus with a:
 - o (i) Glycone portion (pharmacologically inactive) → a sugar (often glucose) that fixes drug to cardiac muscle
 - o (ii) Aglycone portion (pharmacologically active) → exerts drug activity

Anti-arrhythmic effects:

- Prevent and treat atrial tachyarrhythmias (AF, atrial flutter, paroxysmal atrial tachycardia) a/w a rapid ventricular rate → slows AVN conduction to ↓ ventricular response rate

Note – Digoxin should be avoided with:

- (i) DC cardioversion → digoxin should be withheld 24 hrs prior to prevent cardiac arrhythmias (esp VF)
- (ii) Underlying WPW → digoxin enhances conduction through accessory bypass tract (by ↓ its refractoriness) causing VT/VF
- (iii) Ventricular extrasystoles or VT → can precipitate VF (due to ↑ automaticity/excitability)
- (iv) Pts with hypertrophic subaortic stenosis → increased myocardial contractility intensifies resistance to ventricular ejection

Aside – Non-anti-arrhythmic effects (See “Therapy of cardiac arrest, ischaemia and failure”):

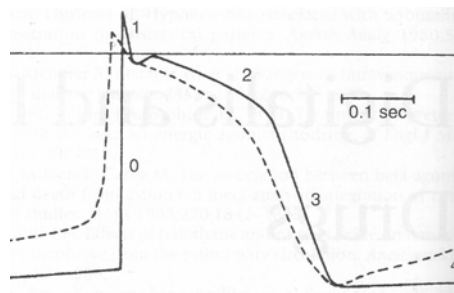
- (1) Treat chronic low-output HF → weak +ve inotrope that improves symptoms and LV performance (↑ C.O.)
- (2) Treat acute ↓ LVF → rarely used b/c ↑ death from sudden cardiac death due to arrhythmias (despite ↓ mortality from HF), and other more potent and less toxic agents available
- (3) Ideal rate control agent for AF in pts with HF → ↓ HR 2° to slowed AVN conduction improves diastolic coronary perfusion and ventricular filling
- Nb. It has minimal effect on ↑ CO in normal heart

Mechanism of action:

- (1) Direct effects on heart
 - o Reversible inhibition of Na^+/K^+ ATPase in sarcolemma of cardiac cell membrane → binds extracellular α -subunit → induces conformational change that interferes with outward Na^+ and inward K^+ transport → results in ↑ $[\text{Na}^+]_{\text{IC}}$ and ↓ $[\text{K}^+]_{\text{IC}}$
 - o ↑ $[\text{Na}^+]_{\text{IC}}$ causes ↓ Ca^{2+} extrusion across a $\text{Na}^+/\text{Ca}^{2+}$ exchanger → ↑ $[\text{Ca}^{2+}]_{\text{IC}}$ → results in +ve inotropy and ↑ force of contraction
 - o ↓ $[\text{K}^+]_{\text{IC}}$ causes – (i) ↑ effective refractory period of AVN → slowed conduction rate through AVN → ↓ HR, and (ii) ↑ automaticity (excitability)

Aside – Effect on cardiac AP:

- Less -ve RMP → ↑ automaticity (excitability)
- ↑ slope of phase 4 depolarisation
- ↓ slope of phase 0
- Shortened phase 2 → ↓ duration of cardiac AP



- (2) Alters ANS activity
 - o Digoxin activates vagal nuclei centrally and sensitises arterial baroreceptor → ↑ PNS activity (↑ ACh effect on cardiac mAChR)

- Causes – (i) ↓ SAN activity, and (ii) prolongs effective refractory period of AVN and slow conduction through it → both causes ↓ HR

Pharmacokinetics:

Absorption	PO (bioavailability > 70%), IM (unpredictable absorption and painful 2° tissue necrosis), IV (rapid absorption)
Distribution	- Minimal protein binding (25%); V_D 5-10 L/kg - [digoxin] at cardiac tissue is 15-30x that of plasma at steady state - Large inactive tissue store in skeletal muscle ([] 8-15x that of plasma)
Metabolism/ Elimination	- Minimal hepatic metabolism (10%) → produces inactive metabolites - Mainly excreted unchanged by kidneys (thus renal dysfunction causes toxicity!) - Elimination $t_{1/2}$ 30 hrs

Pharmacodynamics:

- CVS effects:
 - Dose-dependent ↑ myocardial contractility → ↑ SV → ↑ C.O.
 - Blunts excess SNS a/w compensatory response to HF → ↓ SVR → ↓ afterload → ↑ C.O.
 - Vagotonic effect, ↓ SAN discharge, ↓ AVN conduction → ↓ HR
- Renal effects
 - ↑ RBF/GFR due to ↑ C.O. → ↑ diuresis

Important to note → ECG features of digoxin:

- Prolonged PR interval (delayed conduction through AVN)
- Shortened QTc interval (more rapid ventricular repolarisation)
- Scaphoid ST segment depression (decreased slope of phase 3)
- Flattening or inversion of T-waves

Nb. They do NOT suggest toxicity → they disappear 3 weeks after digoxin is ceased

Digoxin toxicity:

- Digoxin has a very narrow therapeutic index → toxicity occurs in 20% of patients
- Risk factors:
 - (i) Renal dysfunction (as it is cleared renally)
 - (ii) ↓ K^+ (esp with diuretics or ↓ $PaCO_2$ with hyperventilation) → ↑ affinity of digoxin binding to cardiac myocytes
 - (iii) Other electrolyte disturbances – ↑ Na^+ , ↑ Ca^{2+} , ↓ Mg^{2+}
 - (iv) pH disturbances
 - (v) ↑ SNS activity (esp by arterial hypoxaemia)
 - (vi) ↓ skeletal mass (loss of inactive store)
- Features:
 - GI symptoms – Anorexia, N/V, diarrhoea, abdominal pain
 - CNS symptoms – Visual disturbances (deranged red-green colour perception), headaches, confusion, drowsiness, muscle weakness
 - CVS symptoms – Any arrhythmia can occur, although atrial tachycardia with block is more common, while death is usually a/w VF
 - ↑ automaticity – PVBs, atrial and ventricular tachycardias, bigemini, Etc.
 - Delayed AVN conduction – Junctional rhythm and AV heart block
 - Sinus arrest (at high doses) due to SAN block by vagal tone
 - Others: Skin rash and gynecomastia are rare

Note – Plasma digoxin levels usually 0.5-2.5 ng/mL → toxic if > 3 ng/mL (BUT symptoms can occur below this toxic levels, esp when risk factors are present)

- Treatment:
 - o (i) Correct risk factor (I.e. $\downarrow K^+$, $\downarrow Mg^{2+}$, hypoxaemia, Etc.)
 - o (ii) Phenytoin, lignocaine, propranolol $\rightarrow$ treat cardiac arrhythmias
 - o (iii) Atropine and temporary pacemaker $\rightarrow$ treat bradycardia and AV heart block
 - o (iv) Supplement K^+ (assuming normal serum $[K^+]$) to $\downarrow$ digoxin binding to cardiac myocytes
 - o (v) Digoxin-specific Fab (IgG antibodies)
 - Indicated when – Life-threatening arrhythmias, uncontrolled $\uparrow K^+$, plasma digoxin levels > 20 ng/mL
 - Mechanism – Avidly binds digoxin to form a Fab-digitalis complex $\rightarrow$ removed from circulation via renal excretion
 - Issues – Hypersensitivity and anaphylaxis with subsequent use of Fab

Drug interactions with digoxin:

- $\uparrow$ plasma [digoxin] with – Amiodarone, captopril, erythromycin, verapamil, diazepam
- $\downarrow$ plasma [digoxin] with – Antacids, cholestyramine, metoclopramide, phenytoin
- $\uparrow$ arrhythmias with – SCh, pancuronium, β -adrenergic agonists

(g) ***To describe the pharmacology of adenosine with reference to its antiarrhythmic properties.***

Overview of adenosine:

- A naturally-occurring endogenous purine nucleoside present in all cells → consists of adenine (purine base) and D-ribose (pentose)

Antiarrhythmic effects:

- (i) Differentiate SVT vs VT → adenosine transiently slows HR with SVT (but not with VT)
- (ii) Terminate PSVT due to re-entry circuits involving AVN
- (iii) Transiently slows ventricular rate of AF/atrial flutter to aid ECG diagnosis → BUT does not convert it to sinus (as these rhythms are not generated by AVN re-entry)

Mechanism of action:

- Act on Adenosine-1 (A1) receptors at SAN/AVN:
 - o Gi effect (↓ IC cAMP) → opens adenosine-sensitive K⁺ channels (↑ K⁺ current) → hyperpolarises cell and shortens AP duration
 - o Results in slowed conduction through AVN and –ve chronotropy at SAN
- Very short-lived effect (due to ↓↓↓ elimination t_{1/2}) – but its effects are:
 - o Antagonised by methylxanthines (caffeine/theophylline) → inhibit A1R
 - o Potentiated by dipyridamole → inhibit adenosine uptake

Pharmacokinetics:

- Available in IV only → given in incremental doses from 3-12 mg as rapid IV bolus (preferably via central cannula)
- Elimination t_{1/2} < 10 secs → rapidly taken up by carrier-mediated transport into RBC and vascular endothelium → deaminated to inosine

Side-effects:

- Short-lived due to short t_{1/2} but very distressing:
 - o Facial flushing and headache
 - o Dyspnoea and chest discomfort
 - o Nausea
 - o Hypotension
 - o Bronchospasm (avoid if asthma/COPD)
 - o Transient bradycardia, AV heart block and even asystole (as it potentiates effects of ACh on heart)
 - o Induce AF/flutter (as it decreases atrial refractory period)
- Contraindicated if 2nd or 3rd degree AVB, SSS, or AF/flutter (as its effects are dependent on a functional AVN)

(h) ***To describe the pharmacology of magnesium with reference to its antiarrhythmic properties.***

Antiarrhythmic effects:

- (i) Treat intractable VT/VF and Torsades de Pointes (esp due to digoxin, LA toxicity, post-MI, cardiac surgery, and electrolyte imbalance)
- (ii) Treat multifocal atrial tachycardia

Mechanism of action:

- Not entirely clear → but it slows the rate and prolongs the conduction time of SAN, and prolongs the effective refractory period of AVN → possible mechanisms:
 - o A mineral that is an essential co-factor for several proteins – Na^+/K^+ ATPase, Ca^{2+} ATPase, slow-type (L-type) Ca^{2+} channel
 - o Acts as Ca^{2+} antagonist
 - o Inhibits catecholamine release
- Given IV – 2 g over 5 mins → then infuse 1-2 g/hr

Side-effects:

- (i) Hypotension (due to peripheral vasodilation)
- (ii) Muscle weakness → prolongs effect of ND NMBD
- (iii) Somnolence and CNS depression → prolongs effects of CNS depressants
- (iv) Prolongs clotting time and inhibits platelet aggregation
- (v) Inhibits catecholamine release from adrenergic NT and adrenal medulla (at high doses)
- (vi) Others: Flushing, headaches, dizzy, N/V

(i) ***To describe the adverse effects of the anti-arrhythmic agents with particular reference to the potential pro-arrhythmic properties.***

- (1) Torsades de Pointes (aka. polymorphic VT)
 - Most common pro-arrhythmic effect seen with anti-arrhythmics (esp class IA and III)
 - Mechanism – Triggered by early-after depolarisations in setting of delayed repolarisation and increased duration of refractoriness (which manifests as prolonged QTc interval)
 - Exacerbating factors – $\downarrow K^+$, $\downarrow Mg^{2+}$, LVF, concurrent prolonging QTc drugs
- (2) Incessant ventricular tachycardia
 - Generally associated with class IA and IC agents (esp with previous VT and LVF)
 - Mechanism – Slow conduction of cardiac impulses $\rightarrow$ create continuous ventricular tachycardia circuit
 - VT is slowed (due to drug effect) and resistant to drug/electrical therapy
- (3) Wide complex ventricular rhythm
 - Associated with class IC drugs in setting of structural heart disease (esp with excessive plasma levels or abrupt change in dose)
 - Reflect re-entrant tachycardia $\rightarrow$ easily degenerates into VF
- (4) Precipitation of VT/VF in context of underlying WPW
 - Associated with digoxin and CCBs
 - Mechanism – $\uparrow$ conduction through accessory bypass tract
- (5) Bradyarrhythmias
 - Includes – Bradycardia, AV heart block, sinus arrest
 - Associated with adenosine, digoxin, CCB, β -blockers, lignocaine and class III agents

ANTI-HYPERTENSIVE DRUGS

(a) *To classify the mechanism of action of the anti-hypertensive agents.*

(1) Sympatholytics

- (a) Centrally-acting agents (α_2 agonists) – Eg. clonidine, α -methyl dopa
- (b) Ganglion blockers (competitively inhibits nAChR at both PNS and SNS ganglia, and at adrenal cortex) – Eg. hexamethonium, trimetaphan
- (c) Adrenergic neuron blockers (inhibit NA release from post-ganglionic sympathetic (adrenergic) neurons) – Eg. guanethidine, reserpine, metirosine
- (d) Peripheral receptor blockers
 - o α -receptor blockers – Eg. Phentolamine, phenoxybenzamine, prazosin, Etc.
 - o β -receptor blockers – Eg. Atenolol, propranolol, esmolol, metoprolol, Etc.
 - o Combined α and β blockers – Eg. Labetalol

(2) Vasodilators

- (a) Arteriolar vasodilators
 - o Hydralazine
 - o CCB – Eg. verapamil, diltiazem, nifedipine
 - o K^+ channel activators – Eg. minoxidil, nicorandil
- (b) Nitrodilators (via NO as 2nd messenger) – Eg. NO, SNP, GTN

(3) AII inhibitors

- (a) ACEi – Eg. captopril, enalapril, fosinopril, Etc.
- (b) A2RB – Eg. losartan, irbesartan, Etc.

(4) Diuretics (See notes on “Diuretics” for more details)

- (a) Thiazides – Eg. hydrochlorothiazide, indapamide
- (b) Loop diuretics – Eg. frusemide
- (c) K^+ -sparing diuretics – Eg. amiloride, triamterene
- (d) Aldosterone antagonist – Eg. spironolactone

(5) Others

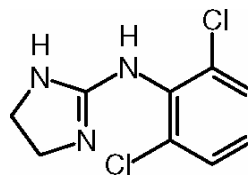
- Magnesium

(b) **To describe the pharmacology of centrally acting agents such as clonidine and alpha-methyl dopa.**

(I) Clonidine:

Overview of clonidine:

- Structure – Aniline derivative
- Presentation – Tablets (100-300 ug), Transdermal patch, Clear colourless solution for IV or neuraxial route (150 ug/mL in HCl form)



Clinical uses of clonidine:

- (1) Treat essential hypertension and acute hypertensive crisis → by ↓ central SNS outflow
- (2) Augment sedation during ventilation of critically ill patient → by CNS depression
- (3) Pre- or peri-operative medication used for – (i) ↓ anaesthetic requirements (↓ MAC and IV induction agent needs), (ii) improve perioperative haemodynamics (Ie. to intubation, surgery, tourniquet-pain) and sympathoadrenal stability (↓ SNS/RAAS response), (iii) post-operative analgesia, (iv) premedication (Ie. anxiolysis)
- (4) Treat acute and chronic pain – (i) neuraxial analgesia, (ii) prolongs effects of regional anaesthesia, (iii) IVRA for chronic regional pain syndromes
- (5) Suppress symptoms of opioid/EtOH withdrawal → by ↓ central SNS outflow
- (6) Treat post-operative shivering → by inhibiting central thermoregulatory control
- (7) Treat post-operative agitation a/w sevoflurane in children

Mechanism of action of clonidine:

- Centrally acting α_2 -agonist (?partial agonist) → 200x ↑ affinity for central α_2 receptors than peripheral α_1 receptors → acts at various locations:
 - o Medullary vasomotor centre → ↓ central SNS outflow → ↓ BP, HR, C.O. and ↑ vasodilation
 - o Pontine locus ceruleus → sedation
 - o Spinal cord → inhibits substance P release, augment endogenous opiate release, modulate descending NAd pain pathways
 - o Various central postsynaptic receptors → MAC sparing effect

Aside – Central α_2 receptors are mainly presynaptic:

- Act via GPCR (G_i) → ↓ IC [cAMP] → opens K^+ channels and promotes K^+ influx → hyperpolarise neuron
- Subtypes:
 - o 2A – Sedation, analgesia, sympatholysis
 - o 2B – Vasoconstriction and antishivering
 - o 2C – Startle response

Pharmacokinetics of clonidine:

Absorption	- PO (rapid absorption in GIT with 100% bioavailability) – 50-600 mcg q8hly dose - IV – 150-300 mcg dose - Topical (via transdermal patch) - Neuraxial – 150 mcg dose
Distribution	- 20% plasma protein bound - V_D 2 L/kg
Metabolism/ Elimination	- Liver metabolism into inactive metabolites (50%); excreted unchanged in urine (50%) - Elimination $t_{1/2}$ 9-18 hrs; Clearance 2-4 L/kg

Pharmacodynamic effects of clonidine:

CVS	- Transient hypertension (due to peripheral α_1 -induced
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	vasoconstriction) → then prolonged ↓ BP (SBP > DBP) → ceiling effect with ↑ dose (due to ↑ peripheral α_1 effect) - ↓ SVR (peripheral vasodilation) with long-term therapy only - BRR intact → no postural hypotension - ↓ HR (causing bradycardia) - C.O. maintained (despite bradycardia) - ↑ coronary blood flow 2° to ↓ coronary vascular resistance (↓ SNS vasoconstrictor tone and ↑ local NO release)
CNS	- Sedation/hypnosis - Anxiolysis (at low doses) and anxiogenic (at high doses) - MAC-sparing effect (up to 50%) - ↓ ICP (due to ↓ MAP/CBF), ↓ CMRO₂ and ↓ IOP (↓ aqueous humour production) - Anti-emetic (↓ CTZ sensitivity)
Pain	- Neuraxial/regional block: ○ Prolongs sensory and motor block a/w LA without ↑ side-effects of LA (but has no inherent sensory/motor block) ○ Provides analgesia w/o side-effects a/w opioids (esp respiratory depression, itch, N/V, urinary retention, Etc.) ○ Acts synergistically with opioids - IV analgesia → ↓ post-operative opioid requirements, obtund tourniquet-induced HTN
Respiratory	Minimal respiratory depression → does not potentiate respiratory depression a/w opioids!
Endocrine	- Inhibits stress response (↓ SNS, catecholamine, RAAS activity) - ↓ insulin release (slightly ↑ BSL)
Haematological	Inhibits SNS-induced platelet aggregation (although α_2 receptors exist on platelets → cause aggregation)
Renal	Diuresis → due to ADH inhibition

Side-effects of clonidine:

- Commonly – Sedation, dry mouth, Na⁺/water retention (needing diuretic)
- Rarely – Skin rash, impotency
- Issues with neuraxial clonidine – Bradycardia, hypotension, sedation, dry mouth. Limited use in obstetric blocks due to foetal bradycardia

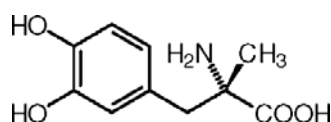
Important to note → Clonidine withdrawal syndrome:

- Occurs when prolonged therapy with large doses (1.2 g/day) are abruptly ceased → induces surge of central SNS outflow causing rebound HTN a/w tachycardia, anxiety, sweating, headaches, abdominal pain
- Treatment – Reinstatement of clonidine, or use vasodilator agents (Eg. SNP, hydralazine, labetalol – but NOT β -blockers alone as they cause unopposed peripheral vasoconstriction and ↑ HTN)
- Prevention – If PO clonidine is to cease (I.e. pre-op), prolonged withdrawal is required (or transfer to clonidine patch)

(II) Alpha-methyl dopa:

Overview of α -methyl dopa:

- Uses – Treat HTN (esp a/w pregnancy) → PO 0.5-3 mg 2-3x/day
- Presentations – Tablet (100-500 mg), Suspension (50 mg/mL), Clear colourless solution for IV (50 mg/mL in HCl formulation with Na metabisulphite preservative)



Mechanism of action of α -methyl dopa:

- α -methyl dopa is lipid soluble $\rightarrow$ crosses BBB $\rightarrow$ decarboxylated and hydroxylated to α -methyl-NAd in adrenergic nerve terminal within CNS
- α -methyl-NAd is a potent α_2 agonist (with limited α_1 agonist activity – 10:1 α_2 : α_1 effect) $\rightarrow$ stimulates presynaptic α_2 receptors within medullary vasomotor centre $\rightarrow$ $\downarrow$ NAd release from nerve terminal $\rightarrow$ $\downarrow$ central SNS outflow

Pharmacokinetics of α -methyl dopa:

Absorption	- PO (as tablet/suspension) – Variable GI absorption and hepatic first-pass metabolism (10-60% bioavailability) - IV (as clear colourless solution)
Distribution	- Lipid soluble (crosses BBB) - $< 20\%$ plasma protein bound
Metabolism/ Elimination	- Conjugated to sulphate as it crosses intestinal mucosa $\rightarrow$ then metabolised in liver to inactive metabolites $\rightarrow$ excreted in urine - 50% excreted unchanged in urine - Elimination $t_{1/2}$ 2.5 hrs

Pharmacodynamic effects of α -methyl dopa:

CVS	- $\downarrow$ SVR $\rightarrow$ $\downarrow$ BP - Postural hypotension (due to loss of BRR) - C.O. unchanged despite relative bradycardia
CNS	Sedation/hypnosis
Endocrine	$\downarrow$ catecholamine and RAA levels in blood
Side-effects	- Rebound HTN with abrupt cessation (less common cf. clonidine) - CVS effects – Significant hypotension (esp with other anaesthetic agents), postural hypotension, bradycardia, and peripheral oedema - CNS effects – Sedation, depression, dizziness, weakness, paraesthesia - GI effects – Deranged liver function, fatal hepatic necrosis - Haematological effects – Autoimmune haemolytic anaemia, thrombocytopenia, leucopenia - Immunological effects – +ve direct Coomb's test (10-20%), eosinophilia with fever, hypersensitivity reactions (myocarditis) - Renal – Dark urine when exposed to air (breakdown of methyl-dopa) - Endocrine – $\downarrow$ PRL release (Eg. gynaecomastia)

(c) *To outline the actions of ganglion blocking agents.*

Types: Hexamethonium and Trimetaphan (both quaternary ammonium compounds)

Uses: Treat essential HTN and acute hypertensive crisis (due to rapid action with short $t_{1/2}$) → no longer used due to unwanted side-effects of ganglia inhibition

Mechanism of action:

- Principle action of ganglion blocking agents → competitively inhibits nAChR at both PNS and SNS ganglia, and at adrenal cortex (but NOT at NMJ)
- Other actions – (i) Directly vasodilate peripheral vessels, and (ii) Release histamine

Effects of ganglion blocking agents:

- Rapid hypotension due to:
 - o 1°ly venodilation of capacitance vessels (↓ preload), but also vasodilation of resistance vessels (↓ afterload)
 - o ↓ C.O. → but this can be offset by reflex ↑ HR
- Histamine release (Eg. bronchospasm, rash, Etc.)
- Unwanted PNS ganglia inhibition – Dry mouth, tachycardia, urinary retention, constipation, mydriasis, raised IOP, Etc.
- Unwanted SNS ganglia inhibition – Postural hypotension, sexual dysfunction

Drug interactions:

- Prolongs effect of NMBD
- Inhibits plasma cholinesterase (↑ duration of SCh, LA, mivacurium, cocaine)

(d) *To describe the pharmacology of agents which act at the adrenergic nerve ending.*

These drugs inhibit NAd release from post-ganglionic sympathetic (adrenergic) neurons

There are 3 main types:

(1) Guanethidine

- Uses:
 - o (i) Effective anti-hypertensive agent (but limited use due to side-effects)
 - o (ii) Control of sympathetically-mediated chronic pain
- Mechanism of action:
 - o Taken up by post-ganglionic adrenergic nerve terminal by “uptake 1 transporter” → displaces NAd from NT vesicles → thereby ↓ amount of NAd released
 - o Acts peripherally only (as it is highly polar and cannot cross BBB → nil central effects)
- Triphasic effect on BP → Initial ↓ BP (direct vasodilation), then transient ↑ BP (displaces NAd from binding sites), then finally ↓ BP (as NAd completely depleted)
- Side effects:
 - o (i) Postural hypotension
 - o (ii) Fluid retention/oedema
 - o (iii) Diarrhoea
 - o (iv) Failure to ejaculate
- Drug interactions:
 - o (i) ↑↑↑ sensitivity to direct-acting sympathomimetics (due to upregulation of adrenoceptors, esp with long-term use)
 - o (ii) ↓ effect with drugs that block uptake 1 transporter (Eg. TCA, cocaine) → prevents uptake of guanethidine

(2) Reserpine

- Use – Formerly used to treat HTN
- Mechanism of action:
 - o Blocks uptake and storage of catecholamines from neuronal cytoplasm in NT vesicles of post-ganglionic sympathetic nerve terminals → leads to de-amination by mitochondrial MAO → depletes NAd, DA and 5-HT throughout body
 - o Acts both centrally and peripherally (as it can cross BBB easily)
- Causes hypotension due to → ↓ C.O. and ↓ SVR (but rarely causes postural hypotension)
- Side effects:
 - o (i) Central effects (depression, lethargy, extrapyramidal symptoms)
 - o (ii) Diarrhoea
 - o (iii) Sexual dysfunction
 - o (iv) Hyperprolactinaemia and galactorrhoea
 - o (v) Gynaecomastia
- Drug interactions:
 - o (i) MAC-sparing agent with inhalational agents
 - o (ii) ↑ sensitivity to direct-acting sympathomimetics (due to adrenoceptor upregulation)
 - o (iii) ↓ sensitivity to indirect-acting sympathomimetics (due to ↓ NAd stores)

(3) Metirosine

- Use – Treat HTN a/w pheochromocytoma
- Mechanism of action – Competitive inhibitor of Tyrosine hydroxylase → ↓ synthesis of catecholamines
- Issues – Severe diarrhoea, sedation, extrapyramidal effects, and hypersensitivity reactions

(e) *To describe the pharmacology of alpha and beta blockers with reference to the management of hypertension.*

(I) α -adrenergic blockers:

- Types:
 - Non-selective (post-synaptic α_1 /pre-synaptic α_2): Phenoxybenzamine, phentolamine
 - Selective (post-synaptic α_1): Prazosin, Terazosin
- Mechanism of $\downarrow$ BP – Antagonism of post-synaptic α_1 receptor $\rightarrow$ dilation of venous > arterial vessels $\rightarrow$ $\downarrow$ preload/C.O. and SVR
- Issues:
 - Post-synaptic α_1 blockade $\rightarrow$ postural hypotension (and syncope), fluid retention, dry mouth, nasal congestion, urinary frequency, sexual dysfunction, lethargy
 - Pre-synaptic α_2 blockade $\rightarrow$ reflex tachycardia, $\uparrow$ +ve inotropy and $\uparrow$ RAAS response (due to lack of –ve feedback of NAd on own release), and $\downarrow$ BGL (due to loss of inhibitory effects of Adr on insulin secretion)

(II) β -adrenergic blockers:

- Types:
 - β_1 selective (Eg. atenolol, metoprolol, esmolol, carvedilol)
 - Non-selective β_1 and β_2 (Eg. propranolol)
 - Intrinsic sympathomimetic activity (Eg. pindolol, acebutolol)
- Mechanism of $\downarrow$ BP – Via β_1 antagonism $\rightarrow$ $\downarrow$ C.O. and SNS-induced RAAS response
- Issues:
 - Non-selective blockade $\rightarrow$ bradycardia, acute LVF, bronchospasm, claudication, masking symptoms of $\downarrow$ BGL and $\downarrow$ glucose tolerance (due to blunting of SNS response to $\downarrow$ BGL), sedation/lethargy, impotence, withdrawal symptoms
 - β_1 selective blockade $\rightarrow$ $\downarrow$ likely to produce bronchospasms (asthma/COPD), impair peripheral blood flow (PVD), or mask symptoms of $\downarrow$ BGL (DM)
 - β -blockers with intrinsic sympathomimetic activity $\rightarrow$ $\downarrow$ bradycardia, -ve inotropy and vasospasms (ideal for pts with bradycardia, LVF, PVD)

(III) Combined α - and β -blocker:

- Type – Labetalol
- Structure – Synthetic salicylamide derivative with 2 asymmetric centres $\rightarrow$ 4 stereoisomers in equal proportions (SR-isomer $\rightarrow$ selective α_1 antagonism; RR-isomer $\rightarrow$ non-selective β effect antagonism)
- Mechanism:
 - Has combined α and β adrenoceptor antagonistic effects:
 - Selective α_1 -antagonism $\rightarrow$ causes $\downarrow$ SVR (due to peripheral vasodilation) $\rightarrow$ $\downarrow$ BP
 - Non-selective β antagonism $\rightarrow$ prevents reflex tachycardia/ $\uparrow$ contractility triggered by BRR in response to $\downarrow$ BP
 - α_1 : β antagonism dependent on route $\rightarrow$ 1:3 PO; 1:7 IV
- Issues:
 - Mainly side-effects of α_1 antagonism $\rightarrow$ 1^oly orthostatic hypotension
 - Side-effects of β antagonism less common $\rightarrow$ bronchospasms, LVF, bradycardia, heart block, nightmares, cramps, Etc.
 - Chronic oral therapy $\rightarrow$ fluid retention (needs diuretic therapy)

(f) ***To describe the physiology and pharmacology of the vascular endothelium and smooth muscle with particular reference to nitric oxide.***

Overview of nitric oxide (NO):

- (1) NO is an endogenous molecule (aka. Endothelium-derived relaxing factor (EDRF)) synthesised throughout the body (Eg. endothelium, neurons, macrophages/PMNL, vascular and skeletal muscle, platelets, Etc.)
- (2) Inhaled NO is used to treat pulmonary HT (following cardiopulmonary bypass or in newborns), treat severe RSHF, treat RDS in premature infants, and improve oxygenation with severe ALI/ARDS
- (3) NO is also a potential contaminant in N₂O cylinders

Production of endogenous NO:

- NO is synthesised from one of the terminal guanidine N-atoms of L-arginine in a reaction catalysed by Nitric Oxide Synthase (NOS)
- NOS belongs to a family of Ca²⁺-activated enzymes with 2 forms:
 - o (i) Constitutive – Present in endothelium (artery > vein), neurons, skeletal muscle, cardiac tissue and platelets → continuously produce NO
 - o (ii) Inducible – Upregulated in endothelium (artery > vein), vascular SM, myocytes, macrophages and PMNLs in response to cytokines/endotoxins → produce large [NO] and related-free radicals → cytotoxicity and ↑ capillary leakage

Mechanism of action of NO:

- NO diffuses from the producing cells (Eg. endothelium, neuron, Etc.) into the target cells (Eg. VSMC, platelet, Etc.) → activates guanylyl cyclase (converts GTP to cGMP) → ↑ IC [cGMP] → activates various protein kinases that cause ↓ IC [Ca²⁺] → various effects (Eg. VSMC relaxation, ↓ platelet aggregation, neurotransmission, Etc.)
- Produces localised effects only due to short t_{1/2} (< 5 secs) → endogenous NO readily binds to Fe²⁺ of haeme-based proteins (esp Hb to form Met-Hb) where it is inactivated

Aside – SNP and organic nitrates (Eg. GTN) exert their pharmacological effects via spontaneous release of NO or metabolism to NO in SM cells

Physiological effects of NO:

System	Physiological effects	Pathophysiology
CVS	- Regulates basal vasodilator tone (and vascular resistance) of systemic and pulmonary arterioles → flow-induced shear stress and pulsatile arterial flow causes continuous local NO production → vasorelaxant effect - Main autoregulatory factor of regional blood flow (esp cerebral and pulmonary BF) → ↑ local NO production by endothelium 2° to ↓ PaO₂ → ↑ CBF and PBF - Direct –ve ino- and chronotropy	- NO deficiency → Essential HTN and cerebral vasospasms after SAH (as NO inactivated by Hb in bleed) - NO excess → Septic shock and cirrhosis (hypotension, hyperdynamic state and ↑ capillary leakage)
Respiratory	- Regulates basal vasodilator tone (and vascular resistance) of pulmonary arterioles → opposes hypoxic-induced pulmonary vasoconstriction - May cause bronchodilation	- NO deficiency → Pulmonary HT
CNS and PNS	- CNS – NO is a NT in neurons within brain/spinal cord → released in response to glutamate excitation of NMDA receptors → role in arousal, pain and memory	- Suppression of NO → ↑ anaesthesia 2° to ↓ CNS excitation (MAC-sparing effect)

	- PNS – NO is a NT in non-Adr/non-cholinergic neurons → controls GI motility (via ENS) and blood flow within corpus cavernosum (penile erection)	- NO excess → Epilepsy, morphine-induced constipation
Haematological and immunological	- Endothelium-derived NO inhibits platelet aggregation/activation - Cytokines/endotoxins stimulate NO synthesis in macrophages/PMNL → degrade phagocytosed pathogens - High avidity for Hb (1500x ↑ cf. CO!)	- NO deficiency → ↑ infection risk, ↑ atherosclerosis 2° to platelet aggregation/vasoconstriction - NO excess → ↑ bleed risk, ↑ inflammation

Clinical use of inhaled NO:

- Indications:
 - o (i) Treat pulmonary HT (following cardiopulmonary bypass or in newborns)
 - o (ii) Improve oxygenation with severe ALI and ARDS
 - o (iii) Treat severe RSHF
 - o (iv) Treat RDS in premature infants
- Mechanism:
 - o (i) Selectively relaxes and dilates pulmonary vessels
 - Inhaled NO diffuses from alveoli to pulmonary vasculature → causes pulmonary arteriolar vasodilation in proportion to degree of pulmonary vascular resistance via aforementioned MOA of NO → ONLY has significant effect on ↓ PVR if there is underlying pulmonary vasoconstriction (I.e. a/w hypoxia)
 - Lacks systemic effects (I.e. hypotension, bleeding) due to rapid metabolism
 - o (ii) Also induces bronchodilation
- Clinical effects:
 - o (i) Bronchodilation
 - o (ii) Improved V/Q matching and PaO₂ (↑ PBF through well-ventilated lung regions)
 - o (iii) ↓ RV pressures, PAP and PVR
 - o (iv) ↑ RVEF and C.O.
- Pharmacokinetics:
 - o Highly lipid soluble → diffuses across membranes readily
 - o Rapidly metabolised (t_{1/2} < 5 secs) → inhaled NO is converted nitrates/nitrites in O₂, and in blood it avidly binds to Hb to form met-Hb
- Delivery:
 - o Dose of 10-40 ppm delivered into inspiratory circuit of ventilatory via a synchronised inspiratory injection system → maintains constant inspired [NO] despite changes in minute ventilation
 - o Requires accurate monitoring via chemiluminescence or electrochemical analysis (accurate to 1 ppm!)
- Side-effects and issues:
 - o (i) Met-Hb → rarely significant unless risk factors present (I.e. children, MetHb reductase deficiency, concurrent oxidising drugs)
 - o (ii) Severe rebound hypoxaemia and PHT with abrupt cessation (thus, wean slowly!)
 - o (iii) Pulmonary toxicity → NO is oxidised to NO₂ (esp with high FIO₂), which is cytotoxic → thus, close monitoring of NO delivery is essential
 - o (iv) Scavenging may be required if unit poorly-ventilated → limit environmental NO levels < 25 ppm for 8 hrs (time-weighted average)

Contraindications – MetHb, ICH, bleeding diathesis, severe LVF
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(g) *To describe the pharmacology of calcium antagonists with reference to the management of hypertension.*

Classes of calcium channel blockers (CCBs):

Class	Type	Actions	Clinical uses	Notable features
I	Phenylalkylamines (Eg. Verapamil)	Cardiac (SAN, AVN, myocardium) >> peripheral arteriolar and coronary artery SM cells	(1) SVT (except WPW) (2) Angina pectoris (3) HTN (4) Coronary vasospasms	Verapamil is a synthetic derivative of papaverine → racemic mixture (L-isomer → CCB effects; D-isomer → LA effect (inhibits fast Na ⁺ channels))
II	Dihydropyridines (Eg. Nifedipine, Amlodipine, Nimodipine)	Mainly peripheral arteriolar and coronary artery SM cells (but NOT venous capacitance vessels)	(1) Angina pectoris (2) HTN (3) Raynaud's syndrome (4) Coronary vasospasms	Nimodipine is a lipid-soluble analogue of nifedipine → pass through BBB to affect cerebral vasculature → used to prevent/treat cerebral arteriolar vasospasms following SAH/migraine
III	Benzothiazepines (Eg. Diltiazem)	Cardiac cells ≈ peripheral arteriolar/coronary artery SM cells	Same as Class I	

Mechanism of action of CCBs:

- Specifically inhibit L-type (slow-type) L-type Ca²⁺ channels within CVS (myocardium, SAN/AVN, and peripheral arteriolar/coronary artery SM cells)

Aside: L-type Ca²⁺ channel is pentameric (α1, α2, β, γ, δ subunits) → α1 subunit forms central part of channel that permits Ca²⁺ influx → CCB bind to α1 subunit

- Binds to cytoplasmic aspect of channel (at α1 subunit), especially when membrane depolarised (channel in opened state) → then maintains channel in a closed/inactivated state → ↓ Ca²⁺ influx → ↓ IC [Ca²⁺]
- ↓ IC [Ca²⁺] causes:
 - (i) Arteriolar and coronary artery SM cell relaxation (inhibits “excitation-contraction coupling” → ↓ Ca²⁺ to bind calmodulin → ↓ Ca²⁺-calmodulin activation of actin-myosin cross-bridging)
 - (ii) ↓ myocardial contractile strength (inhibits phase 2 of cardiac AP cycle, and Ca²⁺-induced Ca²⁺ release from SR for ECC to occur)
 - (iii) ↓ SAN pacemaker rate and AVN conduction velocity (inhibits phase 0 of pacemaker cell AP cycle)

Effects of CCBs:

Effect	Class I (verapamil)	Class II (nifedipine)	Class III (diltiazem)
BP	↓	↓	↓
HR	↓	Reflex ↑ (or nil)	↓
C.O. (myocardial contractility)	↓↓	Reflex ↑ (or nil)	↓
SAN activity	↓↓	Nil	↓
AV conduction rate	↓↓↓	Nil	↓↓
Peripheral arteriolar	↑	↑↑↑	↑↑

vasodilation			
Coronary artery vasodilation	↑	↑↑↑	↑↑

Pharmacokinetics of CCBs:

	Class I (Verapamil)	Class II (Nifedipine)	Class III (Diltiazem)
Absorption	- All are available in PO form. Only class I has IV form - All are well absorbed in GIT (95% absorbed), but have extensive hepatic first-pass metabolism (bioavailability of 20% for class I, 60% for class II, 50% for class III)		
Distribution	90% plasma protein bound	95% plasma protein bound	75% plasma protein bound
Metabolism and Elimination	- 100% hepatic metabolism via demethylation → Norverapamil (active metabolite with anti-arrhythmic effect) - Metabolites excreted in urine (80%) and bile (20%) - Elimination $t_{1/2}$ 6-12 hrs	- 100% hepatic metabolism → inactive metabolites → excreted in urine (80%) and bile (20%) - Elimination $t_{1/2}$ 2-5 hrs	- Hepatic metabolism via acetylation and demethylation (desacetyl- and desmethyldiltiazem) - Excreted in urine (also 40% excreted unchanged) - Elimination $t_{1/2}$ 3-6 hrs

Side-effects of CCBs:

- Headache, flushing, peripheral oedema, N/V, dizziness, systemic hypotension → mainly with class II > III
- Sinus bradycardia (esp if underlying sinus node disease), AV HB (esp if underlying AV nodal block), arrhythmia (VF if underlying WPW), LVF (esp if underlying HF), and cardiac arrest → mainly class I > class III

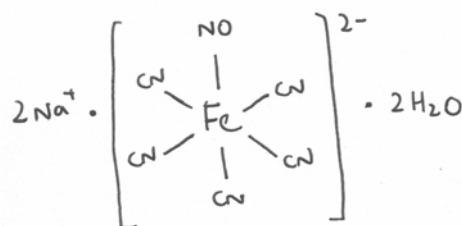
Drug interactions with CCBs:

- (i) Inhaled anaesthetic agents/IV induction agents → augment -ve inotropy, -ve chronotropy and peripheral vasodilatory effects → ↓ C.O., HR and BP
- (ii) β -blockers → same effect as (i)
- (iii) Potentiate non-depolarising and depolarising NMBD → ↓ presynaptic release of ACh
- (iv) LA agents → Class I and III agents have intrinsic LA effect → risk of LA toxicity
- (v) Dantrolene (with use in MH) → ↑ K^+ and CVS collapse
- (vi) K^+ -containing solutions → risk of ↑ K^+ due to blockade of slow IC influx of K^+
- (vii) Digoxin → impairs its clearance → ↑ digoxin toxicity
- (viii) H2RB (cimetidine, ranitidine) → ↓ HBF/hepatic CYP450 activity → ↓ metabolism of CCBs

(h) *To describe in detail the pharmacodynamics and pharmacokinetics of nitroprusside and glyceryl trinitrate including their adverse effects.*

(I) Sodium Nitroprusside (SNP):

Structure of SNP: Inorganic complex $\rightarrow$ ferrous (Fe^{2+}) centre with 5x CN^- and nitrosyl group



Clinical uses of SNP:

- (1) Controlled hypotension for use in anaesthesia $\rightarrow$ rapid and predictable $\downarrow$ in BP
- (2) Management of acute hypertensive crisis
- (3) Management of LVF a/w MR, AR or post-MI
- (4) Cardiovascular surgery
 - o Thoracic aortic aneurysm/dissection or coarctation surgery $\rightarrow$ $\downarrow$ proximal HTN a/w aortic cross-clamping (but risk of spinal cord ischaemia 2° hypotension distal to cross-clamping)
 - o Cardiac surgery $\rightarrow$ treat HTN and PHT

Preparation, administration and dosing of SNP:

- SNP is a lyophilised red-brown powder (50 mg) that is readily reconstituted in D5W (H_2O soluble) $\rightarrow$ form a 0.005-0.02% solution that is straw-coloured with pH 4.5
- Syringe and giving set is wrapped in aluminium foil to minimise sunlight exposure $\rightarrow$ this is b/c sunlight liberates cyanide (CN^-), which causes the solution to turn dark brown or blue $\rightarrow$ solution should be discarded if solution turns colour, is > 8 hrs unshielded or is > 24 hrs shielded
- Hypotensive effect of SNP is very potent, rapid (within 3 mins) and short-lived ($t_{1/2} < 10$ mins) $\rightarrow$ provided by continuous IV infusion (0.5-6 $\mu\text{g}/\text{kg}/\text{min}$) into a vein via a dedicated line with dose carefully titrated to desired BP as per arterial line BP monitoring

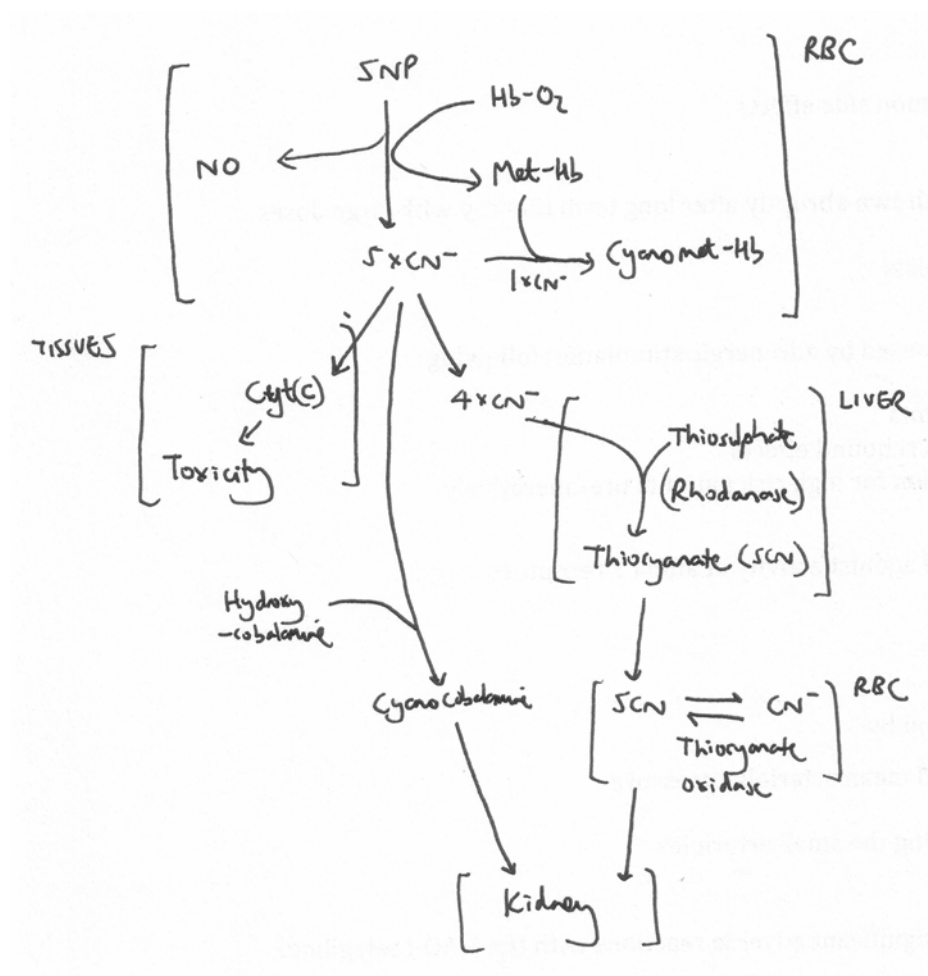
Mechanism of action of SNP:

- SNP is a prodrug $\rightarrow$ it enters RBC where it reacts with Hb-O_2 (e^- are transferred from Fe^{2+} in Hb to SNP) $\rightarrow$ produces (i) unstable SNP radical that breaks down into 1x nitric oxide (NO) and 5x CN^- , and (ii) Met-Hb (oxidised form of Hb)
- NO activates guanylyl cyclase in VSMC in arteries and veins $\rightarrow$ $\uparrow$ IC [cGMP] by converting GTP to cGMP $\rightarrow$ cGMP activates various protein kinases that cause $\downarrow$ IC [Ca^{2+}] by $\downarrow$ Ca^{2+} influx into VSMC and $\uparrow$ sequestration of Ca^{2+} in SER $\rightarrow$ results in relaxation of arterial and venous VSMC $\rightarrow$ arteriolar and veno-dilation

Pharmacokinetics of SNP:

- Available in IV form only
- Short elimination $t_{1/2} (< 10$ mins) $\rightarrow$ brief duration of action needing continuous IVI
- Metabolism of SNP:
 - o SNP enters RBC $\rightarrow$ reacts with Hb-O_2 (whereby electrons are transferred from Fe^{2+} in Hb to SNP) $\rightarrow$ produces (i) unstable SNP radical that breaks down into 1x NO and 5x CN^- , and (ii) Met-Hb (oxidised form of Hb)
 - o Met-Hb combines 1x CN^- $\rightarrow$ forms Cyano-met-Hb (non-toxic)
 - o Remaining CN^- leaves RBC $\rightarrow$ converted in liver and kidney by rhodanase (mitochondrial enzyme) with addition of sulphhydryl group from thiosulphate $\rightarrow$ form thiocyanate (SCN^-) which is less toxic than CN^- and is excreted renally $\rightarrow$ BUT RBC contains thiocyanate oxydase which can reconvert SCN^- back to CN^- !

- CN^- can combine hydroxycobalamin (Vitamin B12) → form cyanocobalamin (non-toxic) → excreted in urine



Pharmacodynamic effects of SNP:

CVS	- ↓ SVR and MAP 2° to arterial vasodilation - ↓ venous return and preload 2° to venodilation - C.O. maintained due to reflex tachycardia and contractility 2° to SNS response from intact BRR (opposes hypotensive effects → prevented with β-blockers) → Nb. with LVF, CO can be maintained due to ↓ preload and afterload without a Δ in HR and contractility - ↓ myocardial MRO_2 and ventricular wall tension - ↓ coronary BF due to hypotension and “coronary steal effect” (healthy vessels dilate and “steal” blood flow away from ischaemic areas that are maximally dilated already)
Respiratory	Inhibits HPV → ↑ V/Q mismatching (esp shunting) and ↓ PaO_2
CNS	- ↑ ICP 2° to ↑ CBF (cerebral vasodilation) - CBF autoregulatory curve shift to left
Endocrine	Reflex SNS and RAAS response to hypotension → high catecholamine and renin/AII/aldosterone levels
Haematological	Inhibit platelet aggregation → ↑ bleeding
GI	Paralytic ileus (due to ↓ mesenteric BF or direct effect)
Side-effects	- Profound hypotension → often a/w dizziness, headaches, N/V, abdominal pain, muscle twitching, palpitations and retrosternal pains → easily reversed with ↓ infusion rate - Tachyphylaxis → due to: ○ (i) Abnormal CN-SCN pathway allows CN^- to accumulate → ↑ CN^--induced stimulation of ↑ C.O. → offsets hypotensive

	effects → need higher dose for effect ○ (ii) Active BRR (esp in young children/adults) → ↑ C.O. → require higher dose for effect - Toxicity 2° to CN⁻, SCN and Met-Hb (see below)
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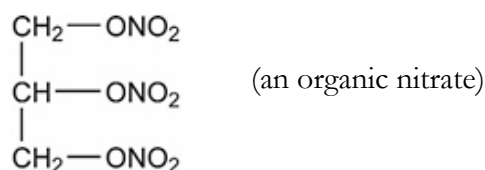
Toxicity associated with SNP:

- (1) CN⁻ toxicity (main)
 - Mechanism – Free CN⁻ binds tissue cytochrome oxidase c → tissue anoxia due to impaired aerobic metabolism via oxidative phosphorylation OP → metabolic acidosis due to lactate produced from anaerobic metabolism
 - Risk factors:
 - (i) Dose > 2 ug/kg/min (esp in young children/adults due to active BRR) → this is b/c liver can clear CN⁻ at SNP dose < 2 ug/kg/min only
 - (ii) ↓ CN⁻ clearance by conversion to SCN by liver (severe hepatic failure, hypothermia, malnutrition, children), renal excretion (severe renal failure), or sequestration to hydroxycobalamine (vitamin B12 deficiency) or metHb
 - Suspect CN⁻ toxicity if:
 - (i) Resistant to hypotensive effects of SNP despite maximal infusion rates or tachyphylaxis (Ie. previously responsive pt is now unresponsive to effects of SNP)
 - (ii) Increased PvO₂ (as tissues cannot utilise O₂)
 - (iii) Metabolic acidosis a/w ↑ lactate (due to anaerobic metabolism)
 - (iv) Symptoms of altered mental status tachycardia, arrhythmias, hyperventilation, sweating, and seizures
 - (v) Plasma [CN⁻] > 8 ug/mL → but use of assay is limited by delay in results, and inaccuracies due to photodecomposition of CN⁻ during analysis
 - Management:
 - (i) Cease SNP infusion
 - (ii) Provide supportive therapy (Ie. 100% FiO₂, correct acidosis with NaHCO₃, Etc.)
 - (iii) Clear CN⁻ from circulation
 - Dicobalt edetate → chelates CN⁻
 - Na thiosulphate → provides additional sulphhydryl groups to convert CN⁻ to SCN
 - Na nitrite or amyl nitrite → convert Hb-O₂ to met-Hb, which has a higher affinity for CN⁻ than cytochrome oxidase
 - Vitamin B12 → complex CN⁻ to cyanocobalamin
 - Prevention:
 - Dose-dependent CN⁻ toxicity occurs at SNP rates > 2 ug/kg/min
 - Toxicity is minimised by – (i) Combining SNP with other anti-hypertensive agents (Eg. CCB, β-blockers, volatiles) to reduce its dose < 2 ug/kg/min, or (ii) Giving prophylactic thiosulphate or hydroxycobalamin when rates > 2 ug/kg/min need to be given
 - Foetal CN toxicity in pregnant patients is prevented by using SNP cautiously → use modest doses for short durations only
- (2) Thiocyanate (SCN) toxicity
 - SCN is cleared slowly by the kidneys (elimination t_{1/2} 2 days)
 - SCN toxicity is less common (cf. CN⁻ toxicity) as it is 100x less toxic than CN⁻ → UNLESS prophylactic thiosulphate is given for prolonged period of time (Ie. ↑ [SCN] produced) or concurrent renal failure (Ie. t_{1/2} ↑ to 7 days)
 - Symptoms of toxicity – Fatigue, tinnitus, N/V, hyperreflexia, confusion, psychosis, coma, seizures
 - Treatment – Dialysis
- (3) Methaemoglobinaemia

- Unlikely to have adverse effects (I.e. impaired oxygenation), even in those with RFs such as met-Hb reductase deficiency, UNLESS a very large dose of SNP given
- Monitor with co-oximetry

(II) Glyceryl Trinitrate (GTN):

Structure of GTN:



Clinical uses of GTN:

- (1) Prevent and treat angina pectoris – due to:
 - (i) ↑ blood flow to subendocardial tissue (2° to large coronary artery vasodilation), without a coronary steal effect (cf. SNP)
 - (ii) ↓ cardiac MRO₂ (2° to ↓ wall tension due to ↓ preload/LVEDP a/w venodilation, and ↓ afterload a/w arteriolar vasodilation)
- (2) Treat LVF a/w MI or post-cardiac surgery → due to ↓ preload (relieves APO)
- (3) Management of acute hypertensive crisis → less potent than SNP; also its effects are dependent on IVV status (as it acts on venous capacitance vessels)
- (4) Controlled hypotension for use in anaesthesia (see above subpoint)
- (5) Biliary and oesophageal spasms → due to GI SM relaxation

Preparation, administration and dosing of GTN:

- S/L aerosol spray (400 ug/metered dose) or tablets (300-600 ug)
- Modified release tablet (buccal – 1-5 mg; swallowed – 2.5-10 mg)
- Transdermal patch (5 or 10 mg/24 hr) → tolerance occurs if left > 24 hrs (prevented by removal after 14-16 hrs). Can explode if left on during DC cardioversion!
- Clear colourless solution (0.5, 1 or 5 mg/mL) diluted in D5W or N/S to 0.01% for continuous IVI at 0.5-5 mcg/kg/min (titrated to effect) → GTN is absorbed by polyvinyl chloride, thus glass bottles and special polyethylene administration sets are used!

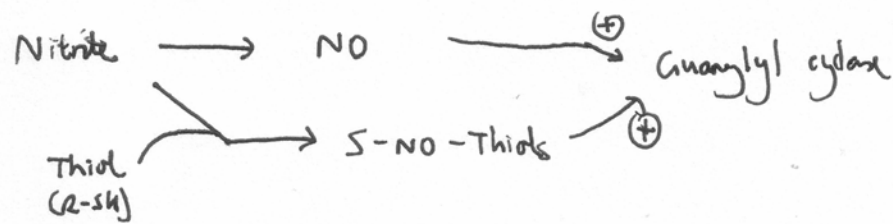
Mechanism of action of GTN:

- NO is liberated from GTN via a thiol-dependent pathway involving nitrate reductase → occurs 1°ly in the liver (see below), but also in vascular SM cells
- NO then activates guanylyl cyclase in VSMC 1°ly in veins (> arterioles) → ↑ IC [cGMP] by converting GTP to cGMP → cGMP activates various protein kinases that cause ↓ IC [Ca²⁺] by ↓ Ca²⁺ influx into VSMC and ↑ sequestration of Ca²⁺ in SER → results in relaxation of venous VSMC (> arteriolar VSMC) → 1°ly veno-dilation (> arteriolar vasodilation)
- Note – Selective venodilating effects may be due to ↑ thiol/sulphydryl groups present in veins (cf. arteries)

Pharmacokinetics of GTN:

- Absorption:
 - S/L and buccal routes – Rapidly absorbed. Limited hepatic first-pass metabolism (as only 15% blood flow to liver). Maximal effects within 30 minutes
 - PO route – Rapidly absorbed in GIT but extensive hepatic first-pass metabolism (bioavailability < 5%)
 - Transdermal route – Slow and sustained absorption
 - IV route – Maximal effect within 2 mins
- Metabolism:
 - GTN is metabolised in the liver (and in vascular SM cells) via a pathway that depends on nitrate reductase and thiols/sulphydryl groups (R-SH)
 - Elimination t_{1/2} 1.5 mins

GTN $\rightarrow$ Glycerol dinitrate + Nitrite (NO_2^-)



Pharmacodynamic effects of GTN:

CVS	- At low doses $\rightarrow$ venodilation of capacitance veins and large coronary artery vasodilation $\rightarrow$ causes: - o $\downarrow$ venous return/preload and ventricular EDP $\rightarrow \downarrow$ wall tension and cardiac MRO₂ - o Variable effect on C.O. $\rightarrow$ usually $\downarrow$ 2° to $\downarrow$ preload, BUT it $\uparrow$ with LVF - o HR unchanged - o Postural hypotension $\rightarrow$ due to $\downarrow$ preload/venous return 2° to peripheral redistribution of blood volume - o $\uparrow$ coronary blood flow to subendocardial areas, without a coronary steal effect - At high doses $\rightarrow$ there is ALSO arteriolar vasodilation of resistance vessels $\rightarrow$ causes: - o $\downarrow$ SVR $\rightarrow \downarrow$ BP (SBP > DBP) and $\downarrow$ afterload $\rightarrow \downarrow$ wall tension and cardiac MRO₂ - o $\downarrow$ coronary blood flow $\rightarrow$ due to $\downarrow$ coronary perfusion pressure and $\downarrow$ filling time (a/w reflex tachycardia) - o $\downarrow$ PVR $\rightarrow \downarrow$ PAP 2° to pulmonary vasodilation
Respiratory	- Inhibits HPV $\rightarrow \uparrow$ V/Q mismatching (esp shunting) and $\downarrow$ PaO₂ - Bronchodilation $\rightarrow$ relaxes bronchial SM
CNS	$\uparrow$ ICP 2° to $\uparrow$ CBF (cerebral vasodilation) – at start of therapy only
Haematological	Inhibit platelet aggregation $\rightarrow \uparrow$ bleeding
GI/GU	- Relaxes oesophageal and GI sphincter SM $\rightarrow$ treat oesophageal and sphincter of Oddi spasms - Relaxes uterine SM
Tolerance	- Tolerance to veno/vaso-dilating effects $\rightarrow$ dose- and duration-dependent (within 24 hrs of continuous treatment) - Due to depletion of thiol/sulphydryl groups within vascular SM cells - Prevented by – (i) Daily drug-free period of few hrs, or (ii) NAC infusion (provides thiol/sulphydryl groups)

Side-effects of GTN:

- Headache and facial flushing (due to vasodilation in face, neck, meninges – common at start of therapy only)
- Sinus tachycardia, postural hypotension and syncope
- Rarely – Methaemoglobinaemia occurs as nitrite metabolite of GTN oxidises Hb-O₂ to met-Hb $\rightarrow$ occurs only with very high doses, prolonged therapy or hepatic dysfunction

GTN is contra-indicated in HOCM and severe AS (due to $\downarrow$ venous return/preload)

(i) ***To describe the pharmacology of the ACE inhibitors and angiotensin receptor antagonists with reference to the management of hypertension.***

(I) Angiotensin-converting enzyme (ACE) inhibitors:

Types of ACEi:

- Group 1 (Captopril) – Active drug that is metabolised into active metabolites
- Group 2 (Enalapril, Ramipril) – Prodrug that increases oral bioavailability prior to activation by hepatic metabolism to a diacid moiety
- Group 3 (Lisinopril) – Active drug that is not metabolised and excreted unchanged in urine

Uses of ACEi:

- (i) HTN 2° to ↑ renin production (esp in diabetics with nephropathy → delay progression of renal disease)
- (ii) Heart failure (remodel myocardium → cause LVH to regress)
- (iii) MI with LV dysfunction (remodel myocardium → cause LVH to regress)

Mechanism of action:

- Competitive inhibitor of ACE causes:
 - o (i) ↓ conversion of AI to AII → ↓ activation of AII receptor (AT₁ subtype – Gq mechanism) → causes ↓ vasoconstriction, ↓ aldosterone release, ↓ Na⁺/H₂O retention, ↓ SNS activation, and ↓ thirst
 - o (ii) ↓ breakdown of bradykinin (endogenous vasodilator substance) → ↑ vasodilation

Pharmacokinetics of ACEi:

- Captopril:
 - o Well absorbed from GIT (bioavailability 65%)
 - o 25% plasma protein bound
 - o Hepatic metabolism (50%) → oxidised to dimer and mixed sulphides; excreted unchanged in urine also (50%)
 - o Elimination t_{1/2} 2 hrs
- Enalapril:
 - o Absorbed PO (enalopril) or IV (enaloprilat)
 - o Prodrug (enalopril) is hydrolysed in liver and kidney into active agent (enaloprilat) → thus should be avoided in pts with liver failure
 - o Elimination t_{1/2} 4-8 hrs → but effect up to 20 hrs due to active agent

Pharmacodynamic effects of ACEi:

- CVS
 - o ↓↓↓ SVR (2° to ↓ vasoconstriction and ECFV) → ↓ BP
 - o ↑ C.O. (2° to ↓ afterload)
 - o HR may ↑ due to intact BRR
 - o Prevents LV remodelling → improve LV function and survival
- Renal – Natriuresis/diuresis, ↓ GFR and RBF (2° to ↓ AII-mediated efferent renal arteriolar vasoconstriction)
- Endocrine – ↓ aldosterone release, compensatory ↑ renin levels (2° to loss of –ve feedback)

Side-effects of ACEi:

- (i) Severe hypotension upon commencement → thus, introduce slowly
- (ii) Acute renal failure (2° to ↓ AII-mediated efferent renal arteriolar vasoconstriction) → use cautiously with renal impairment and concurrent use of NSAIDs/frusemide; contraindicated with bilateral renal artery stenosis
- (iii) ↑ K⁺ (2° to ↓ aldosterone) → avoid if underlying renal failure or concurrent drugs that ↑ plasma [K⁺] (I.e. spironolactone or K⁺-sparing diuretics)
- (iv) Persistent dry cough (2° to bradykinin)
- (v) Life-threatening angioedema (2° to bradykinin)

- (vi) Unexplained hypoglycaemia in DM patients
- (vii) Foetal/neonatal death → contraindicated with pregnancy
- (viii) Rarely: Agranulocytosis, thrombocytopenia, loss of taste, rash, pruritis, Etc.

Important to note – ACEi should be withheld during peri-operative period → a/w ↑ perioperative hypotension that is resistant to crystalloid IVF and sympathomimetics

(II) Angiotensin II receptor blockers (A2RBs):

Examples of A2RBs: Losartan, Irbesartan, Candesartan (often + hydrochlorothiazide)

Uses of A2RBs: Similar to that of ACEi → used when there is an adverse effect a/w ACEi (esp dry cough)

Aside: Benefits of A2RB over ACEi:

- (i) Most specific way of blocking effects of AII at AT₁ subtype receptor → b/c there are non-ACE pathways that can produce AII
- (ii) Does not inhibit cardioprotective properties of AT₂ subtype receptor
- (iii) Fewer side effects (esp dry cough and angioedema)

Mechanism of action: AII receptor antagonist → specific for AT₁ subtype

Pharmacokinetics:

- Good GIT absorption but large hepatic first-pass metabolism (30% bioavailability)
- 99% plasma protein bound
- Hepatic metabolism to active carboxylic acid metabolite (10-40x more potent) and inactive metabolites → excreted in urine and bile; also renal excretion unchanged
- Elimination t_{1/2} 2 hrs (but 7 hrs for active metabolite)
- Note – Dose needs to be ↓ with liver disease

Pharmacodynamic effects and side-effects:

- Similar to ACEi EXCEPT:
 - (i) Less dry cough and angioedema (as bradykinin metabolism by ACE is not affected by A2RBs)
 - (ii) Inhibits –ve feedback on renin → compensatory ↑ renin and AII produced

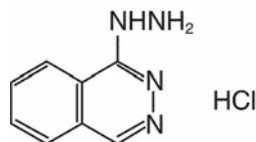
Important to note – A2RBs should be withheld during peri-operative period → a/w ↑ perioperative hypotension that is resistant to crystalloid IVF and sympathomimetics

Like ACEi – Contraindicated with bilateral RAS and pregnancy. To be used cautiously with renal impairment, ↑ plasma [K⁺], and concurrent use of K⁺-sparing agents, NSAIDs and frusemide

(j) ***To outline the pharmacology of hydralazine and the potassium channel activators (nicorandil and minoxidil).***

(I) Hydralazine:

Structure: Pthalazine derivative



Uses of hydralazine:

- (i) Oral form – used for chronic HTN and severe CHF (oral) → given with β -blocker (limits RAAS activation and reflex $\uparrow$ HR 2° to SNS activation) and diuretic ($\downarrow$ oedema)
- (ii) IV form – used for acute hypertensive crisis (esp a/w pre-eclampsia) → effect within 10-20 mins and lasts 3-6 hrs (BUT unpredictable response – prolonged hypotension common)
- acute HTN crisis, esp a/w PET (IV)

Mechanism of action:

- Activation of guanylate cyclase → $\uparrow$ IC cGMP → $\downarrow$ IC $[Ca^{2+}]$ → vasodilation

Pharmacokinetics:

Absorption	- PO (well absorbed but variable hepatic-first pass metabolism → 30% bioavailability with “rapid acetylators”; 50% with “slow acetylators”) - IV (use D5W to prevent rapid breakdown)
Distribution	90% protein bound in plasma; can cross placental barrier
Metabolism/ Elimination	- Hepatic metabolism (85%) via acetylation, hydroxylation and glucuronidation (VARIABLE acetylation in population) → metabolites excreted in urine - Also excreted unchanged in urine (15%) - Elimination $t_{1/2}$ 3 hrs ($\downarrow$ to 45 mins with “rapid acetylators”)

Pharmacodynamic effects:

- CVS
 - $\downarrow$ BP (DBP > SBP) 2° to $\downarrow$ SVR → due to vasodilation of resistance vessels (arterioles) >> capacitance vessels (veins)
 - Absence of postural hypotension → due to selective vasodilation of arterioles
 - Reflex $\uparrow$ HR and C.O. 2° to SNS activation via intact BRR
 - Vasodilation of coronary arteries → $\uparrow$ coronary blood flow
- CNS – Vasodilation of cerebral arteries → $\uparrow$ CBF
- GI/GU – Vasodilation of renal and splanchnic arteries → $\uparrow$ RBF/GI blood flow
- Metabolic – $\uparrow$ renin secretion → $\uparrow$ RAAS activation

Side-effects:

- (i) Oedema 2° to Na^+ /H₂O retention (thus, give diuretic)
- (ii) Reflex tachycardia → can induce angina/myocardial ischaemia (thus, give β -blocker)
- (iii) N/V, vertigo, diaphoresis
- (iv) Rarely: Drug fever, urticaria, peripheral neuropathy, blood dyscrasia (anaemia, pancytopenia)
- (v) Lupus erythematosus type syndrome (esp with LT use, high doses, women and slow acetylators)
- (vi) Foetal tachycardia (crosses placental barrier)

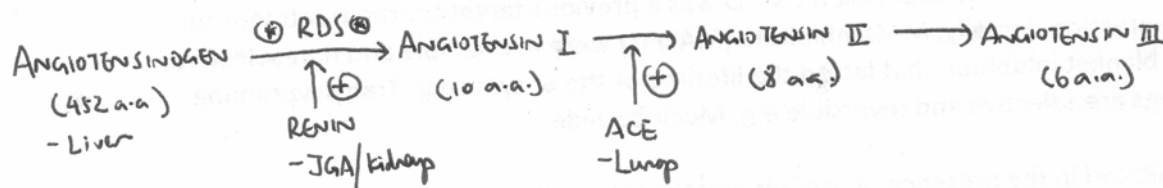
(II) Potassium channel activators:

- (1) Minoxidil
 - Uses – Severe HTN and alopecia
 - Mechanism of action:
 - (i) Activates ATP-sensitive K^+ channels in heart and arterioles → $\uparrow$ K^+ influx (hyperpolarisation) → closes Ca^{2+} channels ($\downarrow$ influx) → $\downarrow$ IC $[Ca^{2+}]$ → arteriolar vasodilation and $\downarrow$ myocardial contraction

- (ii) Activation of guanylate cyclase $\rightarrow \uparrow$ IC cGMP $\rightarrow \downarrow$ IC $[Ca^{2+}] \rightarrow$ vasodilation
 - Pharmacokinetics:
 - PO (well absorbed from GIT with 90% bioavailability) and IV forms
 - Not protein-bound
 - 90% hepatic metabolism; 10% excreted unchanged in urine
 - Elimination $t_{1/2}$ 3 hrs (BUT anti-HTN effect lasts up to 3 days)
 - Pharmacodynamic effect – Same as hydralazine (see above), but anti-HTN effect lasts up to 3 days!
 - Side-effects – Same as hydralazine (see above) except:
 - No lupus erythematosus type syndrome
 - PHT more likely (related to fluid overload)
 - Fluid accumulation in serous cavities (pericardial effusion, cardiac tamponade)
 - Hypertrichosis of face and arm
 - Breast tenderness
- (2) Nicorandil
- Uses – (i) Prevent and treat angina pectoris, (ii) Treat CHF, (ii) Treat HTN
 - Mechanism of action:
 - (i) Activates ATP-sensitive K^+ channels in heart and arterioles $\rightarrow \uparrow K^+$ influx (hyperpolarisation) $\rightarrow$ closes Ca^{2+} channels ($\downarrow$ influx) $\rightarrow \downarrow$ IC $[Ca^{2+}] \rightarrow$ arteriolar vasodilation and $\downarrow$ myocardial contraction
 - (ii) Activation of guanylate cyclase $\rightarrow \uparrow$ IC cGMP $\rightarrow \downarrow$ IC $[Ca^{2+}] \rightarrow$ vasodilation
 - Pharmacokinetics:
 - PO only (well-absorbed with minimal hepatic first-pass metabolism)
 - Minimal plasma protein binding
 - 20% hepatic metabolism (via denitration)
 - Elimination $t_{1/2}$ 1 hr $\rightarrow$ effects last 12 hrs!
 - Pharmacodynamic effects:
 - $\downarrow$ BP – Both venodilation ($\downarrow$ preload) and arteriolar vasodilation ($\downarrow$ afterload)
 - $\uparrow$ C.O. and reflex $\uparrow$ HR
 - Improved coronary blood flow (w/o “steal” phenomenon) – A/w coronary vasodilation and $\downarrow$ LVEDP
 - Cardioprotective against ischaemia
 - Suppresses Torsades de Pointes with prolonged QTc
 - Side-effects – Headaches, aphthous ulcers

Pharm-07B8: Write short notes on anti-hypertensive drugs that exert their action via blocking the effects of angiotensin. 73%

Angiotensin → family of peptide hormones synthesised within “Renin-Angiotensin-Aldosterone” axis:



Majority of activity via AII → acts via AT₁ and AT₂ receptors (GPCR – Gq → activates PLC to ↑ IP₃ → ↑ IC Ca²⁺) to cause:

- (1) Vasoconstriction
- (2) ↑ SNS activity
- (3) ↑ renal tubular reabsorption of Na⁺ and ↑ tubular K⁺ secretion via → (i) Direct effects on the PCT, and (ii) Release of Aldosterone from the adrenal cortex
- (4) ↑ body H₂O content via → (i) ↑ thirst (via hypothalamus), and (ii) ADH secretion (↑ H₂O reabsorption in renal CD)
- (5) ↓ RBF and GFR (esp at ↑↑↑ levels of AII)

Two types of anti-hypertensive drugs that exert action via blocking effects of angiotensin:

	Angiotensin-converting enzyme (ACE) inhibitors	Angiotensin II receptor blockers
Types and examples	- Group 1 (Captopril) – Active drug → metabolised into active metabolites - Group 2 (Enalapril, Ramipril) – Prodrug with ↑ oral bioavailability → later activated by hepatic metabolism - Group 3 (Lisinopril) – Active drug that is not metabolised → excreted unchanged in urine	Losartan, Irbesartan, Candesartan (often + hydrochlorothiazide)
Indications	- (1) HTN 2° to ↑ renin production (esp with DM nephropathy → delay progression of renal disease) - (2) Heart failure (remodel myocardium → cause LVH to regress) - (3) MI with LV dysfunction (remodel myocardium → cause LVH to regress)	Similar to ACEi → used when there is an adverse effect a/w ACEi (esp dry cough)
Mechanism of action	Competitive inhibitor of ACE: - (i) ↓ conversion of AI to AII → ↓ activation of AII receptor (AT₁ subtype) → inhibits AII effects (see above) - (ii) ↓ breakdown of bradykinin	- AII receptor antagonist → specific for AT₁ subtype - Nb. Most specific way of blocking AII effects at AT₁ receptor → b/c there are non-ACE pathways that can produce AII
Pharmacodynamic effects	CVS - ↓↓↓ SVR (2° to ↓ vasoconstriction and ECFV) → ↓ BP - ↑ C.O. (2° to ↓ afterload) - HR may ↑ due to intact BRR - Prevents LV remodelling → improve LV function and survival Renal – Natriuresis/diuresis, ↓ GFR and RBF (2° to ↓ AII-mediated efferent renal arteriolar vasoconstriction) Endocrine – ↓ aldosterone release, compensatory ↑ renin levels (2° to loss of –ve feedback)	Similar to ACEi EXCEPT it does not inhibit cardioprotective properties of AT ₂ receptor
Side-effects	- (i) Hypotension (refractory to IVF and sympathomimetics) → esp during perioperative	Similar to ACEi EXCEPT ↓ dry cough and angiooedema (as bradykinin metabolism by

	period (thus, should be withheld) - (ii) Acute renal failure (2° to ↓ AII-mediated efferent renal arteriolar vasoconstriction) → use cautiously with renal impairment and concurrent use of NSAIDs/frusemide; contraindicated with bilateral renal artery stenosis - (iii) ↑ K⁺ (2° to ↓ aldosterone) → avoid with renal failure or concurrent use of K⁺-sparing drugs - (iv) Persistent dry cough (2° to bradykinin) - (v) Life-threatening angioedema (2° to bradykinin) - (vi) Unexplained hypoglycaemia in DM patients - (vii) Foetal/neonatal death → contraindicated with pregnancy - (viii) Rarely: Agranulocytosis, thrombocytopaenia, loss of taste, rash, pruritis	ACE is not affected by A2RBs)
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