1996a(15): Describe briefly the pharmacology of adenosine and its potential use in anaesthesia

Physicochemical	
Structure	Purine nucleoside Purine base D-ribose
Presentation	IV injection 3mg/ml in NS
Pharmacodynamics	
Use	Differentiate b/n SVT and VT Treatment of SVT (90% efficacy)
MOA	↓**SA & AV node activity** Activate adenosine A_1 receptors → ↑K^+ channel opening → hyperpolarisation Antagonises cAMP-mediated catechol stimulation of vent mm (G_i-PCR stimulation) Negative chronotrope / negative dromotrope
Dose	Rapid IV bolus Initial dose 3mg → then 6mg → then 12mg at 1-2min intervals Paeds 0.0375-0.25mg/kg
Heart	↓SA/↓AV node activity → terminate SVT; unmasks AF/flutter Dose-dependent ↑myocardial BF 2° coronary aa dilatation (A_2 receptor stim^n)
MAP	Nil effect as bolus (initial ↑MAP then ↓MAP) High dose infusion → ↓TPR → ↓MAP
Respiratory	↓PVR in Pts with pulmonary HT ↑MV (↑TV, ↑RR) 2° A_2 stimulation carotid body Bronchospasm → relative contraindication with COAD/asthma
Other	↑CBF → headache, Impending doom Hyperalgesia, chest discomfort Facial flushing N&V Stimulates glycolysis, inhibits lipolysis Profound bradycardia req pacing ↑risk of VF 2° high grade AV blockade → contraindication in Pts with 2°/3° heart block
Pharmacokinetics	
Absorption/Distribution	IV only / Vd not measurable 2° rapid metabolism
Metabolism	Absorbed into RBC → $t_{½\beta}$ 10s Phosphorylated to AMP / deaminated to inosine

Use in anaesthesia:

- Potential use to ↓MAP pre-operatively (as low dose infusion)
- Intr-operative use ↓MAC of isoflurane
- ↓post-op analgesia requirements

By Amanda Diaz

1999a(16): Describe the effects of α_2 adrenoceptor agonists relevant to anaesthesia

General: α_2 adrenoceptors are present on target tissues
- Presynaptically on sympathetic nerve fibres (peripheral)
- CNS / spinal cord (post-synaptic)
- Platelets

α_2 adrenoceptors are GPCR
- **G_i**-coupled adenylyl cyclase inhibition
    - Activation of receptor → ↓**cAMP**

Commonly used drugs:
- Clonidine
- Dexmetatomidine

Actions mediated by receptor activation:

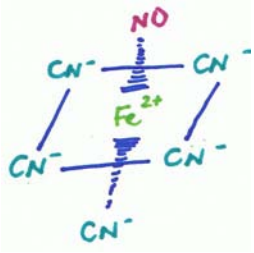
Effect	**Mechanism of Action**
↓MAP	Initial ↑MAP → 2° α_1 stimulation (vasoconstrict) especially with rapid bolus Sustained ↓MAP 2° central α_2 activation (↓NA release) Rebound ↑MAP may occur on removal of drug (2° upregulation NA)
HR/SV/Contractility	0
Analgesia	↓NA release in brain / spinal cord → analgesia Dorsal horn inhibition (Aδ- C-fibre mediated afferents) ↓spontaneous sympathetic outflow Useful as combination in neuraxial/regional blockade as ↓opioid requirement (Dose: 1-2mcg/kg) ↓MAC / ↑LA duration Useful adjunct in chronic pain / opioid withdrawal
Sedation/Anxiolytic	Sedation 2° ↓NA release within brain
Anti-emetic	↓sensitivity of CTZ Anti-sialogogue / ↓intr-gastric pressure (↓LOS tone)
ICP/IOP	↓ 2° ↓MAP (↓CBF), also ↓aqueous, ↓CSF production
Post-op shivering	↓2° α_2 stimulation in spinal cord Can lead to ↓T°C

1999b(2): Briefly describe the mechanisms and treatment of toxicity of SNP

General: Sodium nitroprusside (SNP) is an **inorganic complex** which functions as a **prodrug**

- Acts as a **peripheral vasodilator** indirectly by ↑**NO** production

Mechanism of Action



- SNP → RBC → reacts with **oxyHb** to form **metHb**, **5 cyanide molecules (CN^-)** and **NO**
- **NO** diffuses out to endothelium → activates **guanylyl cyclase** system → ↑**cGMP**
  - cGMP → **prevents Ca^{2+} entry** into smooth muscle cell; also ↑**Ca uptake** into **SR**
  - Effect: **Vasodilatation**
- MetHb binds 1 CN^- molecule → forming non-toxic complex
- 4 CN^- diffuse out of RBC
  - Metabolised by **rhodanase** enzyme in **liver** and **kidneys** to **thiocyanate (SCN)** → by adding sulphur moiety
- SCN: $t_{½\beta}$ 3-4 days
  - 100 x less toxic than CN^-
  - Excreted in urine → ↑in presence of renal failure

Toxicity of SNP

Related to the products of metabolism

NO

- Causes overall ↓MAP by vasodilation
  - Arterial → ↓SVR
  - Venous → ↓preload
- SNP highly potent → careful titration of infusion to effect
  - Requires invasive BP monitoring
- Pulmonary vasodilation
  - Removal of **hypoxic pulmonary vasoconstriction** → ↑shunt
  - Treatment: supplemental O_2
- Cerebral vasodilation
  - ↑ICP but ↓CPP
  - May cause headache
- Platelets
  - ↓platelet aggregation (NO effect)

Cyanide

- May occur with infusions > 2µg/kg/min
- Occurs when **sulphur donors / metHb exhausted**
- CN^- binds **inactive cytochrome oxidase** → inhibiting **oxidative phosphorylation**
  - ↑anaerobic metabolism → **metabolic acidosis**
  - ↓O_2 utilisation → ↑**mixed venous O_2 content**
- Suspect in Pts with HT resistant to therapy
  - ↑HR
  - Diaphoretic, ↑MV
  - Can progress CNS Sx inc seizure, coma

By Amanda Diaz

- ↑risk in **hypothermic** patients
    - ↓rate of rhodanase conversion CN^- → SCN
- Treatment:
    - Cease infusion
    - ↑O_2 available → supplemental O_2
    - Correct acidosis → $NaHCO_3$
    - ↑Sulfur donors → IV Na thiosulfate (150mg/kg over 15min)
    - ↑CN^- binders → hydroxycobalbumin (Vit B_{12a}) → cyanocobalbumin (Vit B_{12})
    - ↑metHb → Na nitrite 5mg/kg slow IV **if severe**

Thiocyanate

- 100 x less toxic than CN^- → toxicity rare
- Excreted renally → in Pts with renal failure, 7-10day infusion of 2-5µg/kg/min can produce toxic levels
- Sx: non-specific
    - N&V, tinnitus, fatigue
- Signs:
    - ↑reflexes, confusion, psychosis, coma
- Treatment: dialysis

MetHb

- Unlikely to accumulate to levels which are toxic, even in Pts with congenital MetHb reductase deficiency
- To develop 10% metHb → need 10mg/kg SNP (really high dose)
- Treatment: methylene blue (1-2mg/kg) BUT not advised as metHb needed for CN^- clearance

Photoreduction

- Must be administered / stored protected from sunlight
- Exposure will cause rapid reaction to form **HCN^-**
    - Colour of solution changes from browny-red → blue
    - Must be discarded

2001a(15): Compare and contrast the pharmacology of esmolol and propranolol

Property	Esmolol	Propranolol
Uses	AF, atrial flutter Peri-operative HT MI	HT, angina, essential tremour, anxiety, thyrotoxicosis, HOCM, Pheo prophylaxis, migraine
Physicochemical		
Presentation	Solution for injection (10/ 250mcg/ml) pH 5.5 (pain on injection)	Tablets (10, 40, 80, 160mg), solution for injection (1mg/ml)
Isomerism	Nil	Racemic mixture S-isomer → most effects R- → prevent $T_4 \rightarrow T_3$
Routes/doses	IV only	PO: 30-320mg/day (bd→tds) IV: 1-10mg
Pharmacodynamics		
Mechanism of Action	Selective β_1 block °sympathomimetic activity Peak effect 10min Off by 20min	Non-selective β_1/β_2 block °Sympathomimetic activity High doses inhibits Na^+ ion flux → membrane stabiliser
CVS	Neg inotrope Neg chronotrope Similar ↓CO to propranolol	Neg inotrope Neg chronotrope ↓CO by ~20% $\downarrow MRO_2$ ↓MAP → poorly defined ?central effect
Respiratory	Minimal effect	$\downarrow FEV_1$ 2° ↑airways resistance ↓ventilatory response to $\uparrow PaCO_2$
CNS	↓CBF 2° ↓MAP → ↓ICP	Cross BBB → ↓tremor, ↓IOP, anxiolytic ↓ICP, ↓vasospasm
GU	Nil	↓uterine tone
Metabolic	Min	↓renin (β_1 block JGA)→ ↓aldosterone ↓FFA ↓gluconeogenesis
Side Effects	Less likely to produced HF, Heart block	HF, heart block Bronchospasm Nightmares Mask Sx ↓BSL ↓exercise tolerance Abrupt cessation → angina, V arrhythmias, MI, sudden death
Drug interactions	↑recovery time from sux (5-8min)	Displace fentanyl from lungs
Pharmacokinetics		
Absorption	IV only	90% PO Bioavailability 30% 2° 1^{st} pass metabolism
Distribution	Lipid soluble (+++) 60%protein bound Vd 3.5L/kg	Lipid soluble (+++) 95%protein bound (AAG) Vd 3.5L/kg
Metabolism	Plasma hydrolysis→ red cell	Hepatic metabolism: oxidative

By Amanda Diaz

	esterase Major acid metabolite has weak β-blocker activity	deamination → dealkylation → glucoronidation 4-hydroxy metabolite active ↓dose in liver failure
Elimination	Renal: <1% unchanged CL 285ml/min/kg $t_{½β}$ 10min Renal disease → caution major acid metabolite renally excreted ($t_{½β}$ 3.5hrs)	Renal: <1% unchanged CL 1L/min $t_{½β}$ 3hrs Nil effect renal failure

2002a(13): What are the side effects of amiodarone? What problems develop during concurrent anaesthesia?

Physicochemical:

- Amiodarone is a benzofuran derivative
    - 37% iodine by wt → resembles **thyroxine**

Presentation

- Tablets: 100/200mg
- Injection: 30/50mg/ml

Pharmacodynamics:

Use

- Treatment of SVT, VT, WPW syndrome

Mechanism of Action

- Has Class I, II, III, IV activity
- Slows rate of repolarisation by blocking K^+ channels
    - ↑duration of action potential
    - ↑refractory period
- Partial antagonism (non-competitive blockade) of α- and β-agonists
    - ↓receptor numbers
    - Inhibits coupling of receptor to regulatory subunit of adenylate cyclase system

Side-Effects

Pulmonary

- Common (5-15%)
    - Incidence 10% at 3yrs
- Pneumonitis, fibrosis, pleuritis
- Reversible if stopped at early stages
- Acute pulmonary toxicity: mimics infectious pneumonia (uncommon)
    - ↑risk of acute toxicity with high FiO_2 as in anaesthesia
- ↑risk of developing post-op ARDS in critically ill Pts
    - Especially if on CPB

Cardiac

- Large doses, rapid IV → bradycardia, ↓MAP
    - 2° α/β blockade → vasodilatation
- **GA may exacerbate effect**
    - **Sinus arrest, complete AV block, ↓TPR, ↓MAP, ↓CO, HF**
        - **Can be resistant to atropine, adrenaline and norad**
        - **May require peri-operative pacing**
- ↑QT (2° class III blockade)
    - ↑risk ventricular dysrrhythmias (Torsades de Pointes) → less common than with sotolol
    - Care in concurrent use with TCA, thiazides, phenothiazine

Thyroid

- Can precipitate hyper-/hypothyroidism → related to iodine content
- Incidence 2-4%
    - ↑ or ↓T_4 production
    - Prevents peripheral conversion of $T_4 \rightarrow T_3$

        - Replacement should be T_3
- Usually reversible with cessation

Liver
- Cirrhosis, hepatitis, jaundice
- Deranged LFTs common → dose-dependent

Skin
- Slate grey appearance 2° photosensitive skin reactions.
    - Reversible on cessation

Gut
- Metallic taste

CNS
- Peripheral neuropathy; rarely myopathy
- Corneal microdeposits common → ?clinical sig
    - Reversible

Interactions
- 95% Protein bound
    - Displaces other highly protein bound drugs (warfarin, phenytoin)
- Digoxin levels and toxicity more common

2002b(7)/2001b(15): Outline the potential advantages and disadvantages of intra- (& peri-) operative beta blockade

General: β blockers are used to treat HT, pheochromocytoma, portal HT, and HF

- Mechanism of action: ***Competitive*** blockade of β adrenoceptor, preventing activation by endogenous adrenaline/NA
  - ***Some*** exhibit ***partial agonist*** properties (useful in HF)
- Can be ***selective*** for β_1 receptor or ***non-specific*** (β_1 and β_2 blockade)
- Most of the wanted effects occur with β_1 blockade:
  - Negative inotropy
  - Negative chronotropy
- Unwanted effects arise from β_2 blockade
  - ↓MAP 2° ↓CO
  - Orthostatic hypotension
- In general, ***short acting β_1 selective blockers*** are used in anaesthesia in the peri- and intra-operative period due to ↓β_2 related side-effects
  - Metoprolol
  - Esmolol

Advantages	**Disadvantages**
↓Myocardial Work ↓***O_2 demand*** of heart mm 2° ↓HR, ↓contractility	↓***MAP can be refractory to treat*** Unable to oppose cardiac effect of β blockade
↑Diastolic time ↑coronary aa perfusion time → improved LV perfusion ↑***O_2 supply*** ↓systolic time 2° ↓HR	***Unopposed vagal tone*** → eg from peritoneal stretch, laryngoscopy is unopposed results in profound ↓MAP difficult to treat Bradycardia
Anti-arrhythmic Effect β blockers are class II anti-arrhythmic Stabilises myocardium Sotolol also class III anti-arrhythmic	***Drug Interactions*** ***α_1 agonist*** (metaraminol) to treat ↓MAP → ↑↑MAP→ ↑risk MI ***Ca^{2+} blockers*** → can precipitate HF/heart block
↓MAC	Bradycardia
Obtunds hypertensive response to Intubation Tourniquet	Negative inotropy/chronotropy effect ***Precipitate CCF*** → APO LVF in susceptible Pts
	Mask hypoglycaemia ↓response to ↓BSL (catecholamines, glucagon) in diabetics
	Bronchospasm especially in asthmatics
	Masks signs of inadequate anaesthesia/analgesia in Pts

2002b(8): Outline the pharmacological effects of vasopressin
General: Vasopressin is the synthetic form of the hormone **ADH**
ADH:

- Nonapeptide; produced in **hypothalamus**, secreted by **posterior pituitary**
- Stimulated by **change in osmolarity** of blood (2° ↑osm / ↓circulating vol)
- Effect:
    - **V_1 receptors**: GPCR
        - Present in **vascular smooth muscle** / **platelets**
        - ↑Phospholipase C → ↑DAG / IP_3 → ↑Ca
        - ↑SVR, ↓renal arteriolar vasoconstriction (efferent > afferent → maintain GFR)
    - **V_2 receptors**: GPCR
        - **Collecting duct** → ↑**aquaporin insertion** into luminal membrane → ↑H_2O absorption
        - 2° effect → ↑urea reabsorption to ↑osmolarity of renal medulla → ↑H_2O movement through aquaporins
    - **V_3**: Anterior pituitary → ↑ACTH release

Vasopressin:

- Synthetic nonapeptide, ADH analogue
- Administration:
    - IV for evaluation
    - DDAVP available for **intranasal administration** → 1° V_2 effects
        - Preferred drug for management of diabetes insipidus (minimal vasoconstrictor effects)
- Dose: Inotrope 1 – 4IU/hr
    - Arrest: 40IU bolus

Pharmacodynamics

- Uses:
    - Rx ADH-sensitive **diabetes insipidus**
        - polyuria, polydipsia
        - Central cause: ↓ADH secretion by posterior pituitary → 2° trauma / surgery
        - Nephrogenic: ↓inability for kidney to respond to ADH → not treatable with exogenous ADH
    - Premed as infusion in Pts with von Willebrand's disease (DDAVP) to ↑circulating vWF
    - Management of **uncontrolled haemorrhage** with oesophageal varices
- MOA: Stimulation of V_1 and V_2 receptors
    - V_1: present in **vascular smooth muscle** → stimulation → vasoconstriction; most pronounced in **splanchnic** vasculature (↓portal circulation) → high doses required. Renoprotective
        - Not antagonised by β blockers / denervation
    - V_2: CD and distal DCT of renal tubules → ↑aquaporin insertion
- CVS:

    - ↑MAP 2° vasoconstriction
        - ↑SVR
        - Pallour 2° cutaneous vasoconstriction
    - Coronary artery vasoconstriction → angina; MI; ventricular dysrhythmias
        - Even at low doses
        - ↓coronary blood flow
- GIT: ↑peristalsis; N&V; abdo pain
    - 2° stimulation GI smooth muscle
- Uterine tone ↑ with large doses
- Renal: ↑water reabsorption 2° aquaporin insertion
- Coagulation:
    - ↑**factor VIII** (**vWF**) → useful in management of **haemophilia** especially perioperatively
        - MOA unknown
- Allergy / Anaphylaxis
    - Rare → 2° Synthetic
    - ↑use → Antibody formation → ↓duration of action of drug

Pharmacokinetics

Absorption: Nil PO availability → rapid metabolised to amino acids via **plasma / GI proteases**

Distribution: ?

Metabolism: Peptidases to amino acids

- prolonged use → antibodies → ↑breakdown → ↓efficacy

Elimination: recycled in amino acid pool

2003a(7): Classify diuretics, briefly explaining their mode of action

Class	Mode of Action
Osmotic Diuretics (mannitol) Use → rapid ↓ICP	Freely filtered at glomerulus, not reabsorbed → ↑osmolality of filtrate → ↓H_2O reabsorption → ↑urine vol
Loop diuretics (frusemide) Use CCF to ↓oedema, renal failure	1° action in thick ascending limb of LoH Impair Na^+/Cl^- reabsorption → impairs action of counter-current mechanism → ↓hypertonicity of medulla → ↓H_2O reabsorption in collecting duct → ↑vol urine, ↓conc urine
Thiazide diurectics (HCT) Use moderate HT	1° action of early DCT, impair Na^+ / Cl^- reabsorption ↑Na^+ / Cl^- → ↑H_2O excretion Late DCT → ↑Na^+ exchange with K^+/H^+ → hypokalaemic hypocloraemic alkalosis
Aldosterone antagonist (spironolactone)	Competitive antagonist of aldosterone ↓K^+ excretion (K^+ sparing) principal cells → ↑Na^+ / H_2O excretion
K^+ sparing (amiloride)	Block Na^+/K^+ exchange in late DCT independent of aldosterone → ↑Na^+ excretion, ↓K^+ excretion, ↓H_2O reabsorption
Carbonic anhydrase inhibitors (acetazolamide)	Weak diuretic only Non-competitive inhibitor of CA in PCT → ↓conversion CO_2 + H_2O to H_2CO_3 then HCO_3^- and H^+ →↓Na^+/H^+ exchange → ↑Na^+ /HCO_3^- excretion + diuresis → hyperchloraemic acidosis
Others→ not classically identified as diuretics as 1° mode of action is anti-HT ACE inhibitor (-oprils) ATII inhibitors (-sarten)	Mild K^+ sparing effect (see above) Prevent conversion of ATI → ATII 1° in lungs Antagonise ATII

2003b(6): List the potential clinical uses of α_2 adrenoceptor agonists and outline the limitation of clonidine for each

General: α_2 adrenoceptors are present on target tissues
- Peripheral sympathetic nerve fibres (**presynaptic**)
- CNS: Brain and spinal cord (**postsynaptic**)
- **Platelets** (limited role in anaesthetic practice)

Action of α_2 receptor activation
- **G_i**-protein coupled receptor
- Activation → ↓adenylyl cyclase activity → ↓**cAMP** production

Clonidine
- partial agonist of α_2 adrenoceptor (limited α_1 activity)
- Available for oral, IV, epidural use

Clinical uses for α_2 agonists

Use	**Limitation of clonidine**
↓**MAP** Central inhibition (↓SNS outflow) ↓NA release peripherally	Causes transient ↑MAP (2° initial α_1 stimulation) → ↓HR (baroreceptor reflex) especially with bolus dose Prolonged refractory ↓MAP Rebound ↑MAP on cessation 2° upregulation of NA with chronic use
Analgesia (neuraxial, multi-modal) Dorsal horn inhibition → ↓Aδ- C-fibre afferent activity Augments endogenous opiate release	Analgesia $^{w}/_{o}$ respiratory depression Synergistic ^{w}/opioid in neuraxial blockade Nil motor / sensory blockade Ceiling effect (partial agonist) Dose limited by side-effects
Sedation (pre-med) Central inhibition	Slow-acting – unsuitable as sole sedating agent (~90min) Useful as ↓**MAC** of VA (dexmetatomidine is more selective α_2 agonist → ↓↓MAC)
Anxiolytic (pre-med) Central inhibition	Ceiling effect Slow-acting (~90min to peak IV) At high doses ↑anxiety
Blunt BP responses to operative stimuli (LMA insertion, tourniquet HT) ↓**sympathetic outflow** **Modulates afferent pain fibres**	Relatively long-time to act (~90min IV, 3hrs PO) Ceiling effect Dose limited by side-effects
Anti-sialogogue / ↓intra-gastric P ↓**ICP/IOP** (pre-med) **Post-op shivering** **Anti-emetic** Central inhibition ↓sympathetic outflow ↓CBF (↓MAP) ↓aqueous / ↓CSF production	Long time to peak effect Long elimination $t_{½}$ 9-18hrs Partial agonism (ceiling effect) Side effects Large Vd (2L/kg) Causes ++ dry mouth → can be useful

2004a(6): Outline the circulatory effect of GTN

Physicochemical:
- Organic nitrate
- Presentation:
  - S/L spray 400mcg/dose
  - S/L tablets 300-600mcg
  - Buccal tabs 1-5mg
  - Oral tablets 2.6-10mg
  - Patch 5-15mg/24hrs
  - Injection 1-5mg/ml → diluted to 100mcg/ml (0.01%)

Mechanism of Action:
- Metabolised to NO
- NO activates guanylyl cylase → ↑cGMP → ↓Ca^{2+} influx into vascular smooth mm / ↑Ca^{2+} uptake into smooth ER
- Overall ↓Ca^{2+} in cytoplasm → relaxation smooth mm → vasodilatation

Vessels:
- 1° venodilatation
  - ↓tendency for VR
  - ↓preload RV
- Vasodilation
  - ↓end-diastolic pressure / ↓vent wall tension → ↓afterload

Heart:
- ↓metabolic O_2 requirements
  - 2° above factors → ↓myocardial work → ↓O_2 demand
- ↑coronary BF
  - 2° ↓vent wall tension (↓afterload), redirecting blood flow to subendocardium
  - 2° coronary vasodilatation → improve O_2 supply
- Results in favourable ↑supply:demand ratio
- CO
  - ↓VR → ↓CO in normal Pts
    - HF Pts → ↑CO 2° ↓SVR and improved myocardial performance

Periphery:
- Vasodilatation
  - Orthostatic hypotension
  - High doses → ↓systemic vascular resistance (SVR)
    - ↓MAP more pronounced in volume depleted
- Pulmonary
  - ↓PVR → ↑capacitance of pulmonary vessels → favour absorption transudate
  - Release of hypoxic pulmonary vasoconstriction → ↑shunt
- Cerebral
  - ↑CBF/↑ICP 2° vasodilatation
    - Headache common
- Uterus
  - ↓uterine tone
  - ↑blood flow → ↑risk haemorrhage

Haematological
- Rarely precipitates metHb
- Platelets → ↑cGMP → ↓Ca^{2+} in cytoplasm → ↓platelet aggregation

2004a(7): Describe the mechanisms of action of inotropes and give examples

General: The heart is a demand pump which is tonically innervated by sympathetic and parasympathetic nervous system

SNS

- **Stimulation** of the heart
  - Chronotropy (↑HR)
  - Inotropy (↑contraction)
  - Automaticity
  - Lusitropy
  - Dromotropy (AV node conduction)

Parasympathetic Nervous System

- Provides tonic inhibition of heart
- CNX (vagus nn)
- Mediated by ACh (M_2-AChR)

Inotropes

- Agents which when administered ↑**force of contraction (FOC)** of myocardium (↑inotropy) *without altering preload or afterload*.
- May also exert other SNS effects (chronotropy, dromotropy, preload/afterload)

Mechanism of Action

- FOC of myocardium dependent on intracellular [Ca^{2+}] with action potential
  - MOA of inotropic agents → ↑$[Ca^{2+}]_i$
- cAMP: Intracellular messenger → ↑activation intracellular proteins by activating protein kinases → ↑opening of Ca^{2+} channels → ↑$[Ca^{2+}]_i$
  - ↑cAMP production
    - Stimulation of G_sPCR → ↑cAMP → ↑Ca^{2+}
  - ↓breakdown of cAMP
    - Metabolised by phosphodiesterase (5 subclasses) PDE3 important in cardiac muscle
- ↑[Ca^{2+}]
  - Inhibition of exchange pumps
  - Direct ↑Ca^{2+}
- Ca sensitiser
  - Sensitise troponin C as well as mitochondrial, smooth muscle ATP dependent K channels

↑cAMP production

Direct β-adrenoceptor stimulation:

- Adrenaline, Noradrenaline, Dobutamine, Ephedrine, Phenylephrine, Isoprenaline
- ↑Ca^{2+} via β_1 receptor stimulation → G_s-protein activation → ↑adenylyl cyclase → ↑cAMP

Indirect β-adrenoceptor stimulation (↑NA release at nerve terminal)

- Displacing NA from vesicles into cytoplasm resulting in carrier-mediated diffusion into synaptic cleft
- ↓*uptake 1*

By Amanda Diaz

    - inhibition by MAO in nerve terminal
- Ephedrine

Glucagon

- GPCR stimulation → ↑cAMP
- Limited use in β blocker overdose

Histamine

- G_s-protein stimulation → ↑cAMP
- Nil useful cardiac role

↓cAMP breakdown

Phosphodiesterase (PDE) Inhibitors:

- Aminophylline (non-specific), Milrinone (PDEIII)
- Inhibit PDE → ↓breakdown of cAMP (cGMP) → effective ↑cAMP

↑Ca^{2+}

- Glycosides (digoxin)
    - Inhibit Na^+/K^+-ATPase → ↑$[Na^+]_i$ → Impair Na^+/Ca^{2+} exchange pump → ↑$[Ca^{2+}]_i$
- Calcium
    - IV administration → transient ↑inotropic effect
    - Indicated only in ↑K^+/circulatory collapse

Ca sensitising Agents

- Levosimendan
    - ↑Ca interaction with troponin C → enhance contractility without ↑intracellular Ca
    - Activate ATP-dependent K channels on mitochondrial membrane → protect muscle from ischaemia → ***ischaemic preconditioning***
    - ATP-dependent K channel of smooth muscle → vasodilation
    - Long-acting active metabolite
    - Improvement morbidity compared with dobutamine, nil change 30 day survival

2004b(8): List the classes of drugs used clinically to treat left ventricular failure. Outline their mechanisms of action

General: LVF occurs when the **left ventricle** is **unable to meet** the **metabolic demand** of the **systemic circulation** without ↑central venous pressures

- Temporal relationship: >2 weeks

Classes of drugs used to treat LVF

↓Afterload

ACE-I / ATII receptor antagonist

- ↓SVR (↓angiotensin II, III) AT_1R vascular smooth muscle → ATII effect
- ↓circulating catecholamines → ATII effect
- ↑Na / H_2O excretion → ↓Aldosterone action (small ATII)
- ACE found in lung
    - Converts ATI (proprotein) → ATII (vasoconstrictor)
    - ATII → ↑aldosterone release from adrenal cortex
    - Aldosterone → ↑Na/H_2O reabsorption from DCT / CD
    - ATII may also have a direct effect on Na/H_2O retention
- Caution: causes K retention → consider concomitant therapy with K losing diuretic
- Evidence LV remodelling after AMI

Arterial vasodilators

- Prazosin (α blocker) → not effective in heart failure
- Ca channel blockers → ↓afterload but ↓LV function

↓Preload

Diuretics

- ↓circulating vol → ↓preload
    - Most act on renal tubules
- Loop diuretics (frusemide) most commonly used
    - Prevent Na/K/2Cl ATPase in ascending LoH
    - Non-K sparing

  ** ↓ preload before diuretic effect → useful in APO
- Thiazides
    - ↓Na / H_2O reabsorption in early DCT
    - Need good renal function
- Aldosterone antagonist (Spironolactone)
    - In severe LVF
    - Weak Aldosterone competitive antagonist → ↓H_2O reabsorption CD
- K sparing diuretics (amiloride)
    - DCT blockade Na/H_2O reabsorption independent of aldosterone effect

Nitrates (venodilators)

- Peripheral venodilation → ↑venous capacitance
- Liberate NO → stimulates guanylyl cyclase → ↑cGMP
    - cGMP → prevents Ca entry into cell from cytoplasm; ↑Ca uptake into SR
    - Overall effect → ↓Ca availability for muscle contraction → vasodilation

- Tachyphylaxis without ‘drug holiday’

↑Contractility

Digoxin

- Cardiac glycoside
- Inhibition of Na/K ATPase
- ↓conduction at AV node / ↓HR / ↑contractility (weak positive inotrope)
- Nil improvement on mortality, improvement in morbidity

Milronone (PDEIII inhibitor)

- ↓breakdown cAMP → ↑contractility, ↓SVR
- Good for short term management; ↑mortality with long term use

Mixed Effect

β blockers Metoprolol / bisoprolol / carvedilol

  - Stimulation β_1 adrenoceptor → ↑adenylyl cyclase activity → ↑cAMP → protein phosphorylation / activation protein kinases

- Block β adrenoceptors
  - β_1 – myocardium
    - Negatively inotropic / chronotropic
      - ↓MRO_2 myocardium, improve diastolic time
    - Improves O_2 supply / demand ratio
  - β_1 – JGA
    - ↓renin release (↓activation RAA system)
- Cardioselective β blockers (those above) have evidence to improve survival
  - Ratio of β_1 / β_2 blockade important

Although negatively inotropic → improved cardiac function / survival

2005a(7)/2000a(11)/1997a(11): Outline the main biochemical events involved in noradrenergic transmission. Outline how these may by altered by the use of MAO-I

General: Noradrenergic (NA) transmission occurs in

- **postganglionic sympathetic** nerve fibres <u>excluding</u> those innervating
  - sweat glands
  - skeletal mm blood vessels to produce vasodilatation
- CNS cerebral neurones → mood / spinal modulation of pain

NA synthesis and transmission

- NA is stored in vesicles in the nerve terminal of postganglionic fibres (present as varicosities along the axon)
  - NA is pre-synthetised into vesicles in the nerve terminal

Phenylalanine –*phenylalanine hydroxylase (liver)*→ Tyrosine –*tyrosine hydroxylase (cytoplasm)*→ DOPA –*DOPA decarboxylase (cytoplasm)*→ Dopamine –*dopamine β-hydroxylase (cytoplasm)*→ NA

- Arrival of action potential causes opening of voltage-gated Ca^{2+} channels → exocytosis of vesicles
- NA is removed from the synaptic cleft by
  - Binding to postsynaptic receptors α and β (> affinity for α receptors)
    - GPCR
  - Binding to presynaptic receptors (α_2 receptors)
    - Negative feedback / inhibition of further NA release by↓Ca^{2+} influx
  - Reuptake into presynaptic neurones (major mechanism)→ 1° *uptake 1*
    - Broken down by MAO to intermediaries
    - Resynthesised into vesicles
  - Diffusion out of cleft (*Uptake 2*)
    - Small amount of breakdown in synaptic cleft and tissues by COMT directly to **normetanephrine**
    - Intermediaries broken down in circulation by COMT to VMA and DOMA
- NA is metabolised sequentially by:
  - Monoamine oxidase (MAO) → present in nerve terminals
    - Located on outer mitochondrial membrane
    - 2 subtypes: MAO-A (deaminates NA, serotonin, adrenaline); MAO-B (deaminates phenylethylamine, tyramine)
  - Catechol-O-methyltransferase (COMT) → other tissues

Role of MAO → catalyses **oxidative deamination**

- Converts NA into physiologically inactive **deaminated derivatives**
  - 3,4-dihydroxymandelic acid (**DOMA**)
  - **DHPG**
- The derivatives enter circulation and are metabolised by COMT forming
  - **VMA**
  - **MHPG**
- Which are excreted in urine

MAO-I: Antidepressant in Pts resistant to other forms of therapy

Types:

Selective (MAO_A-I) → Selegeline / **Non-selective** (MAO_A-I, MAO_B-I) → Iproniazid

Competitive → moclobemide / **Non-competitive** (covalently bonds MAO) → Selegeline

MOA: Forms complex with MAO (especially cerebral neuronal)

Pharmacodynamics:

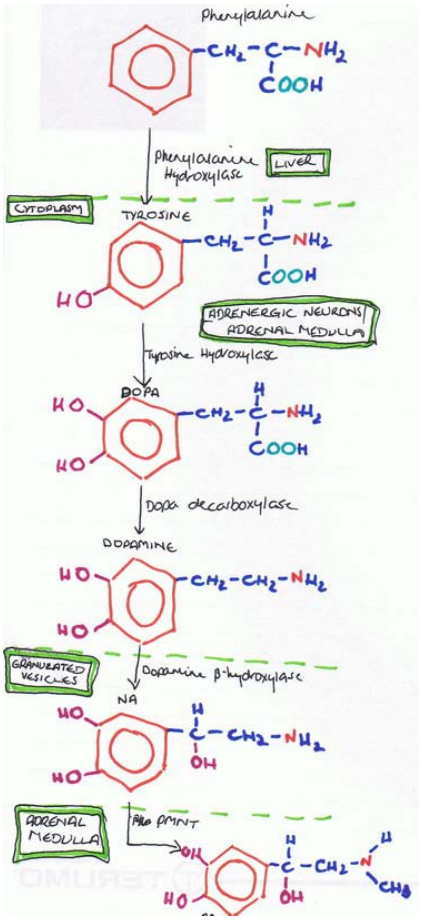
- ↑NA within nerve terminal → ↑NA within vesicles available for release
  - ↑activation of post-synaptic adrenergic receptors
- ↑SNS activity: ↑HR, ↑T°C, mydriasis
- ↑CNS activity: Agitation, seizures → coma
- ↓MAP: 2° false neurotransmitter accumulation (**octopamine**) in cytoplasm of sympathetic nn terminals

By Amanda Diaz

- Less potent vasoconstrictor than NA

Drug Interaction:

- Opioids, sympathomimetics, TCAs, antidepressants, fluoxetine
  - ++ NA accumulation
    - Causes HT, CNS excitation, delirium, seizures, death
- VA: ↑VA requirements (↑MAC)
- Tyramine rich foods → Not broken down in GIT, instead absorbed → ↑production of NA → ++accumulation



2005b(8): Describe the adverse effects of β-adrenoceptor antagonists

General: β adrenoceptors are a group of **G_s protein coupled receptors**

- Stimulated endogenously by: NA, adrenaline

β adrenoceptors are classified into β_1 and β_2

- β_1: myocardial muscle cells (also JGA)
  - Stimulation: ↑adenylyl cyclase → ↑**cAMP** → ↑intracellular Ca^{2+}
  - Stimulation results in: positive inotropy, chronotropy, dromotropy, lusitropy
  - Renal: ↑renin production → ↑ATII (constriction), ↑aldosterone (Na^+ retention)
- β_2: smooth muscle of blood vessels (veins, arterioles); CNS; adipose tissue; internal urethral sphincter; bronchial smooth muscle
  - Stimulation (smooth muscle): ↑adenylyl cyclase → ↑**cAMP** → inhibition of MLCK
  - Stimulation (elsewhere): ↑adenylyl cyclase → ↑**cAMP** → ↑Ca influx
  - Results in: vasodilatation, venodilatation, heightened arousal, ↑BSL, lipolysis, glycogenolysis
  - Also present on GIT, eye

β adrenoceptors antagonists inhibit the activation of the β adrenoceptor

- Uses:
  - CVS: treatment of HT, angina, peri-myocardial infarction
  - Other: Pheochromocytoma, ↑thyroidism, HOCM, Glaucoma
- All are **competitive antagonists**
  - **Selectivity**: β_1 and non-selective (β_1 β_2)
    - β_2 mediates unwanted effects
    - β_1 selective (cardioselective): Atenolol, esmolol, metoprolol
  - Some are **partial agonists** (intrinsic sympathomimetic activity)
    - Unable to illicit full response despite adequate receptor occupancy
    - Less likely to induce bradycardia and heart failure
    - Carvedilol, bisoprolol
  - **Membrane stabilising** properties
    - Minimal clinical significance at therapeutic doses
- Effects:
  - Heart: Negative inotropy/ chronotropy/ dromotropy/ lusitropy, ↓SA node automaticity, ↓AV node conduction
    - ↑CorP time → ↑O_2 supply to myocardium
    - ↓MRO_2
    - In Pt with LVF → may precipitate HF (rare for the selective β_1 antagonists and partial agonists) as ↓CO
    - Inappropriate bradycardia, orthostatic hypotension (↑with ↓blood vol)
  - Class 2 anti-arrhythmic
    - Useful in AF
    - Sotolol can produce unwanted arrhythmia (torsades de pointes)

- Circulation: Overall ↓MAP
  - ↓HR → ↓CO
  - β_1 blockade at JGA → ↓RAA → ↓vasoconstriction, ↓aldosterone production
  - Presynaptic β_2 blockade → ↓NA release
  - In elderly → may cause orthostatic hypotension
  - In anaesthesia → refractory hypotension, ↓effectiveness of vasopressors
- Respiratory: Bronchoconstriction/spasm (β_2 blockade)
  - ↑in asthmatics
  - Can ↑sensitivity of airway to instrumentation
- Metabolic: Non-selective blockade
  - Non-diabetic: Obtund normal response to exercise / hypoglycaemia
    - Mask catecholamine related Sx of ↓BSL
  - Diabetic: ↑resting BSL. Should not be used with oral hypoglycaemic agents
  - Lipid metabolism: ↑trigs, ↓HDL
- CNS: Lipid soluble agents (propranolol, metoprolol)
  - Anxiolytic
  - May cause: depression, hallucinations, nightmares, paranoia, fatigue
  - ↓IOP → good for glaucoma
- GIT:
  - Dry mouth, GI disturbance
- Urinary retention
- Uterine relaxant (propranolol): risk uterine atony

All side-effects are more pronounced in Pts undergoing anaesthesia

2006a(1): Outline the pharmacological management of bronchoconstriction in acute severe asthma. Include mechanisms of action and potential adverse effects

General: Asthma is a **chronic disease** characterised by **airways hyperresponsiveness**

- ↑Bronchial smooth muscle tone → bronchoconstriction
- ↑Mucous production
- Acute attack → gas trapping / ↑physiological dead space

Acute management bronchoconstriction

Supplemental O_2

- ↑FiO_2 → ↑alveolar O_2 in areas undergoing gas exchange
- Adverse effects:
    - Removal of **hypoxic pulmonary vasoconstriction** to non-ventilated units → ↑shunt → ↓O_2 content of blood

Adrenaline: Non-specific α/β adrenoceptor agonist

- Route: Nebulised (direct airways, ↓systemic effects); IM; IV
- Dose: 1mg neb; 1mg IMI
- MOA:
    - β_2 agonist effect: G_iPCR → ↑adenylyl cyclase → ↑cAMP → ↓Ca
        - ↓bronchial smooth muscle tone → ↓airways resistance
        - ↓mucous production → ↓airways resistance
- Adverse Effects: 2° α/β agonist effects systemically
    - α_1: peripheral vasoconstriction → ↑BP; cutaneous constriction (pallour); difficulty with obtaining venous access
    - β_1: ↑HR, precipitate arrhythmias
        - ↑MRO_2 → ischaemia
    - Nausea, abdominal pain
    - ↓insulin → ↑BSL

Salbutamol: Selective β agonist ($\beta_2 > \beta_1$)

- Route: Nebulised
- Dose: 5mg neb
- MOA:
    - Non-selective β agonist, nebulised further ↓systemic effects
    - GPCR → ↑adenylyl cyclase → ↑cAMP → ↓Ca
        - ↓bronchial smooth muscle tone
        - ↓secretions
- Adverse Effects: related to systemic β agonist effects
    - β_1: ↑HR; palpitations
    - β_2: stimulation of skeletal muscle → tremour
        - sweating
        - postural hypotension (vasodilator)
    - Removal of hypoxic pulmonary vasoconstriction → needs supplemental O_2
    - ↓K^+ by ↑intracellular shift
    - N&V
    - ↑BSL

Ipratropium Bromide: Anticholinergic (Atrovent)
- Route: Nebulised
- Dose: 500µg
- MOA: Competitive inhibition of mAChR (M3) on bronchial smooth muscle → GPCR → blockade → ↓phospholipase C → ↓DAG, IP_3 ↓Ca
    - ↓bronchoconstriction effect of vagal stimulation
    - Inhibit ACh enhancement of mediator release from mast cells
    - Nil change in secretions
- Adverse Effects:
    - Minimal systemic effects via neb
    - Unpleasant taste

Corticosteroids: Minimal effect in acute setting as onset ~6-8hrs after admin
- Route:
    - PO: Prednisolone 1mg/kg
    - IV: Hydrocortisone 100 – 300mg tds
- MOA: Bind to intracellular receptors to augment gene transcription / translation
    - ↓inflammatory mediators: ↓phosphlipase A_2 production → ↓arachidonic acid → ↓PG / leukotrienes / IL production
        - ↓leakiness of capillaries → ↓oedema
- Adverse Effects:
    - ↑BSL (↑gluconeogenesis)
    - Adrenal suppression → inhibition of hypothalamic-pituitary-adrenal axis → Addisons → must wean if high dose > 5 days
    - Loss of subcutaneous connective tissue
    - ↓platelet aggregation (↓arachidonic acid → ↓TXA_2) → ↑bleeding

Methylxanthines: Theophylline / aminophylline
- Route: IV / PO / PR
- Dose:
    - PO: 900mg divided doses
    - IV 5mg/kg bolus; infusion 0.5mh/kg/hr
- MOA: Phosphdiesterase III inhibitor
    - ↓breakdown of cAMP → ↑cAMP → ↓Ca → bronchial relaxation
    - ↓influx Ca into smooth muscle → stabilises membrane
    - Antagonises adenosine effect on mast cells → stabiliser
- Adverse Effects:
    - CVS: positive inotrope/chronotrope → ↑CO; ↓SVR → ↓BP
        - Arrhythmogenic at high doses → VF
    - Inhibition of hypoxic pulmonary vasoconstriction → supplement O_2
    - CNS stimulant → ↑risk seizure; ↓CBF
    - ↑gastric acid production
    - ↓gastric motility
    - Diuretic → ↓Na reabsorption; ↑K excretion (hypokalaemia)
    - Narrow therapeutic index

Volatile Anaesthetic Agents
- Route: inhaled

By Amanda Diaz

- MOA: ↓smooth muscle tone NANC (non-adrenergic, non-cholinergic)
- Adverse effects:
    - Minimal if in the course of anaesthetic
    - ↑fraction → ↓BP

Helium (Heliox)

- MOA: Lower density (and specific gravity) than air / O_2
    - During turbulent flow → ↑velocity cf O_2
    - ↓work of breathing
    - Improves oxygenation
- Adverse Effects:
    - Minimal
    - Needs to be on machine
    - ↓inspired O_2 cf O_2 alone

Magnesium

- Route IV
- Dose: 20mmol
- MOA: Smooth muscle relaxation → Ca channel blockade → ↓Ca
    - ↓neutrophilic burst rate → ↓inflammatory mediator release
- Adverse Effects:
    - Sedation
    - Hypocalcaemia

2006b(1)/1998a(14): Describe the use of different sympathomimetics to treat hypotension occurring as a result of a subarachnoid block. Outline the advantages and disadvantages of each of these agents

General: SNS made of pre- and post-ganglionic fibres
- Pre-ganglionic: arise from lateral horns of spinal cord → anterior rami → sympathetic chain / Splanchnic nerve
- Post-ganglionic: Unmyelinated → spinal nerve grey rami

SNS supply:
- Heart → tonic stimulation to oppose tonic parasympathetic control (T1-4)
- Blood vessels → tonic constriction of vessels
- Lungs → bronchial smooth muscle tone
- Coeliac ganglion (gut, kidney)
- Superior/inferior mesenteric ganglion (descending colon, bladder, genitals)

Subarachnoid (spinal) Blockade
- Administration of a LA / opioid cocktail into intrathecal space
  - Blocks transmission of:
    - Sympathetic B fibres (small unmyelinated post-ganglionic fibres)
    - Aδ- and C-fibres +/- motor blockade
  - Level of bloackade is dose-dependent
- Removal of SNS stimulation will result in:
  - Heart (high block ~T1-4): ↓chronotropy, ↓dromotropy, ↓inotropy, ↓lusitropy
    - ↓SV → ↓CO
  - Blood vessels: venodilation, vasodilation
    - ↓tendency for VR (↓preload) → up to 75% of blood volume can be taken up by venous capacitance system
    - ↓TPR (↓afterload)

Management of ↓MAP 2° subarachnoid blockade

Drugs can be classified by:
- Type of receptor activation (α/β)
- Direct /indirect action
  - Direct stimulation of adrenoceptors
  - Indirect stimulation of adrenoceptors via ↑NA release
    - All non-endogenous sympathomimetics have this effect >>ephedrine

Action	Advantages	Disadvantages
Mixed α/β agonists: ↑TPR (vasoconstrict) α_1 effect ↑VR (venoconstrict) α_1 effect → limited ↑CO (↑HR, contractility, SV) β_1 effect		
Adrenaline Direct α/β stim	Low dose infusion→ β effects 1° → ↑CO, ↑corP High dose/bolus → α_1 1° → ↑TPR/↑VR → useful in arrest Short acting No tachyphylaxis	↓MAP 2° β_2 stimulation (↓TPR) Need CVC for infusion Must be diluted
Ephedrine Direct α/β Indirect ↑NA release 1. Eph transported to nn terminal thru *uptake 1* → displace NA from vesicles into cytosol → some degraded by MAO, rest release via <u>carrier-mediated diffusion</u> into cleft (Ca-independent as not exocytosis)	Easy to draw up (1:10) Rapid onset (1-2min) ↑corP Not metabolised by MAO/COMT Relatively long duration of action ($t_{½\beta}$ 4hrs) Peripheral IVC OK Nil effect uterine BF	Tachyphylaxis (NA depletion in terminals) Arrhythmogenic Renal dependent excretion

2. Eph inhibit *uptake 1* 3. Eph inhibit MAO		
Dopamine Direct α/β Indirect ↑NA release	Low dose infusion → β_1 1° → ↑CO, ↑corP → ↑NA release High infusion → α 1° → ↑TPR / ↑VR ↓Arrhythmogenicity cf adrenaline	Infusion Difficult titratability b/n low (<10mcg/kg/min) and high (>10mcg/kg/min) Interact MAOI Need CVC Short acting (10min)
α_1 agonists Peripheral vasoconstriction → ↑TPR → ↑MAP ↑VR (venoconstriction)		
NA (α_1, min β) ↑TPR / ↑VR	Duration action 30-40min ↑CorP	Reflex ↓HR 2° baroreceptor reflex → ↓CO Rapidly metabolised (MAO/COMT) Arryhthmogenic
Metaraminol (1° α_1, min β) Direct/indirect ↑TPR	1:20 dilution Rapid onset (1-2min) Relatively long action (1hr) ↑coronary BF (indirect) Nil effect uterine BF	Reflex ↓HR 2° baroreceptor reflex → ↓CO Rapid ↑MAP → LVF in susceptible Pts
Phenylephrine Nil β effect	Not arrhythmogenic	Reflex ↓HR → ↓CO ↓uteroplacental BF
β_1 agonists: Stimulate myocardium (↑CO); Nil effect TPR		
Dobutamine		Not countering original mechanism for ↓MAP

Uptake 1: high affinity for NA, relatively low max rate of uptake
Uptake 2: low affinity for NA, higher max rate of uptake (Accumulates adrenaline and isoprenaline)

2006b(7)/05b(5): Outline the drug and non-drug Rx of ventricular fibrillation in an adult. Briefly describe their mechanisms of action and potential adverse effects. DO NOT discuss BLS, airway therapies & O_2

General: Ventricular fibrillation (VF) is a life threatening tachyarrhythmia
- Rapid, irregular ventricular activation
- No mechanical effect
- Nil peripheral pulses → cardiac arrest
- ECG: Wide complex QRS, nil p waves

Aim:
- CEASE IRREGULAR RHYTHM
- MAINTAIN PERFUSION OF IMPORTANT ORGANS

Electrical defibrillation
- Only effective treatment → **attempt 1st**
- 1 shock
  - Biphasic 200J
  - Monophasic 360J
- Aim: Terminate irregular rhythm

Drug Therapy

Adrenaline → **1st line drug**
- 1mg, repeated every 3 minutes

MOA: α / β agonist → 1° action in arrest
- α_1: GPCR → ↑phospholipase C → ↑DAG, IP_3, Ca^{2+}
  - ↑SVR 2° vasoconstriction
  - ↑CBF / ↑coronary blood flow

Adverse Effects
- Minimal in the arrest setting

Antiarrhythmics → **2nd line**

Amiodarone: Class 3 antiarrhythmic
- 300mg

MOA: Partial antagonist α / β receptors
- ↑cardiac AP 2° ↑K^+ channel opening
- Class 1 properties → ↓opening fast Na channels
- Class 4 properties → ↓opening Ca channels (↓plateau)

Adverse Effects
- AV node block → 3° blockade
- If hypolakalaemic → ↑risk arrhythmias

Lignocaine: Class 1b antiarrhythmic
- 1.5mg/kg

MOA: Blockade of fast Na channels → ↓rate of depolarisation, ↓peak
- Membrane stabiliser

Adverse Effects
- Less effective at terminating arrhythmias than amiodarone

Others

Vasopressin: synthetic ADH→ **not part of resuscitation algorithm in Oz**

MOA: Agonist V_1 receptors ↑phospholipase C → peripheral vasoconstriction

Adverse Effects: Coronary artery vasoconstriction

$NaHCO_3$

MOA: Reverse acidosis (metabolic acidosis 2° ↑anaerobic metabolism)

- Correct $\downarrow K^+$

2007b(8): Write short notes on anti-hypertensive drugs that exert their action by blocking effects of angiotensin

General: Activation of RAA system important in response to ↓circulating vol

- Ultimate aim to ↑Na/H_2O reabsorption in DCT/CD (1° Aldosterone effect)
- ↑SVR (afterload) → vasoconstriction → maintain MAP (1° ATII effect)

Chronic HT 2° inappropriate activation RAA system

- renal artery stenosis → ↓afferent arteriolar pressure → ↑renin release by JG cells
- reset (↓activity) high pressure baroreceptors (carotid sinus, aortic arch) in setting of chronic HT → prevent inhibition renin release

AntiHT

ACEI

- Pharmacokinetics: 3 groups
    - Active drug metabolised to active metabolites → *captopril*
    - Prodrugs activated by hepatic metabolism → *ramipril*
    - Active drug excreted unchanged in urine → *lisinopril*
- MOA: prevent conversion ATI → ATII (and less potent ATIII)
    - ↓aldosterone release
    - ↓peripheral vasoconstriction
- Use:
    - HT & CCF
    - ↓mortality in HF assoc with MI 2° ↓cardiac remodelling
- Side effects:
    - Prevents breakdown of kinins (eg bradykinin)
        - Persistant cough
        - Angioedema
    - Rash
    - Headache
    - ↑K
    - ↑renin levels (ATII acts part of negative feedback inhibition)
- Drug interactions:
    - NSAIDs → critical ↓renal afferent arteriole → precipitate renal failure
    - ↑↑K with K-sparing diuretics

Angiotensin II receptor antagonist (irbesarten)

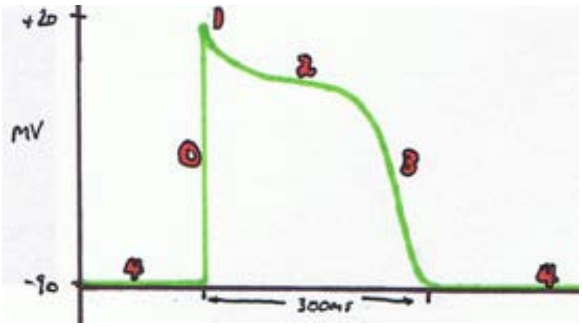
- MOA: competitively inhibit AT_1 receptor
    - Adrenal cortex → ↓aldosterone release
    - Peripheral vessels → prevent vasoconstriction
    - Some direct ATII receptors on DCT/CD
- Use:
    - As with ACEI
    - ↑renin (2° blocking ATII negative feedback) → ↑↑ATII levels
    - Better tolerated in those with kinin related S/E → cough, angioedema
- AT_2R remains unblocked
    - May possess cardioprotective properties

MAKEUP: Discuss how anti-arrhythmic drugs affect the cardiac action potential

General: Classically, anti-arrhythmic agents have been classified according to the **Vaughan-Williams Classification** which was based on microelectrode studies on isolated cardiac fibres

- Based on effect on cardiac action potential (specific ion channel blockade)
- Largely historical
- Found many anti-arrhythmic agents do not fit into one class only (eg amiodarone belongs to class I, III, IV
- Some do not fit into classification
    - Digoxin
    - Adenosine

Myocardial Action Potential



Phase 0: Opening of **fast inward Na channels**

Phase 1: Spike

- Closure of fast Na channels

Phase 2: Plateau

- Opening of **L-type Ca channels**

Phase 3: Repolarisation

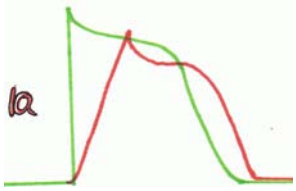
- Complete closure of Na channels; closure of Ca channels
- Opening of K channels → inward movement
- Active pumping of Na out of cell, Ca into SR

Phase 4: Diastolic potential

- remains at RMP in non-pacemaker cells

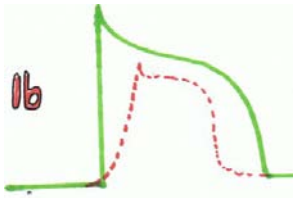
Class 1

- Block **fast inward Na channels**
- **Membrane stailisers**



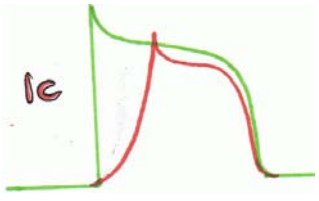
Class 1a: Procainimide; Quinine

- Membrane stabilisers → ↓excitability of non-nodal regions
- Effect on AP:
    - ↓slope phase 0
    - ↓height of spike
    - ↑duration AP → ↑QT / QRS
    - Prolongs refractory period



Class 1b: Lignocaine, phenytoin

- Stabilises membrane → ↓spontaneous phase 4 depolarisation outside atria → ↓aberrant beats (eg ventricular dyrhythmias)
- Effect on AP:
    - Little effect phase 0
    - ↓height of spike
    - ↓duration AP
    - Shortens refractory period



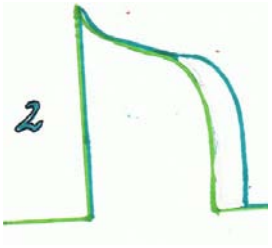
Class 1c: Flecainide

- Membrane stabilisers → suppress re-entrant rhythms

By Amanda Diaz

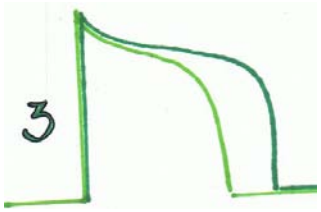
- Effect on AP:
    - ↓phase 0 depolarisation
    - Nil effect duration AP → °effect refractory period

Class 2 *esmolol, metoprolol, atenolol, propranolol, sotolol*



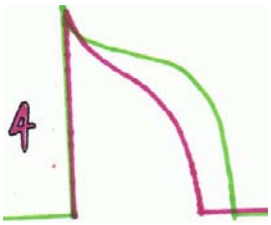
- Exert effect on **pacemaker cells** and ↓**conduction AV node**
- ↑refractory period, ↓automaticity
- Effect on AP:
    - Nil change phase 0
    - ↓conduction velocity
    - ↑refractory period

Class 3 *amiodarone, sotolol, bretylium*



- **Block K channels**
- ↑↑↑refractory period → suppress re-entrant rhythms
- Effect on AP:
    - Nil change phase 0
    - ↑duration AP
    - ↓automaticity
    - ↑QT

Class 4 *Verapamil, Diltiazem*



- **Block L-type Ca channels**
- ↓automaticity SA node, ↓impulse propagation AV node
- Effect on AP:
    - Nil change phase 0
    - ↓phase 2 plateau
    - ↓AP duration

MAKEUP: Discuss IV fluids

	pH	Osmolarity	Electrolytes		Sugar	Elimination
Saline Solutions						
0.9%	4.5 – 7	304 mOsm	Na 150	Cl 150	0	-
3%	5.6	1000 mOsm	Na 500	Cl 500	0	-
7.5%	5.6	2567 mOsm	Na 1283	Cl 1283	0	-
Dextrose Solutions						
5%	4	252 mOsm	0		50g/L Glucose	$t_{½\beta}$ 30min
4%D 1/5NS		310 mOsm	Na 30	Cl 30	40g/L Glucose	$t_{½\beta}$ 30min
Hartmann's (CSL)						
	5 – 7	274 mOsm	Na 129	Cl 109	0	-
			K 5	Ca 2		
			Lactate 29			
Mannitol						
20%	5 – 7	1098 mOsm	0		100g/L Mannitol	$t_{½\beta}$ 72min
Albumin						
4% (50g/L)		290 mOsm	Na 140	Cl 128	0	$t_{½\beta}$ 24hrs
20% (250g/L)						
Dextrans (fermenter sucrose)						
70		300 mOsm	Na 150	Cl 150		$t_{½\beta}$ 6hrs
40 (anaphylaxis 1:3000)		300 mOsm	Na 150	Cl 150		$t_{½\beta}$ 2hrs
Synthetic Colloids						
Gelofusin MW 30kDa	7.4	274 mOsm	Na 154	Cl 120		$t_{½\beta}$ 3hrs
Haemocell MW 35kDa	7.3	301 mOsm	Na 154	Cl 154		$t_{½\beta}$ 3hrs
			K 5.1	Ca 6.25		
Anaphylaxis: 1:1000 Excreted renal (80%); bile (10%) Care with blood transfusions (citrated blood) → Ca will ↑clotting						

MAKEUP: Discuss the pharmacology of α_1 antagonists. Compare and constrast phentolamine, phenoxybenzamine and prazosin

General: α-adrenergic antagonists bind selectively to α-adrenergic receptors

- prevent activation by catecholamines
    - cardiac and peripheral vasculature

	Phentolamine	**Phenoxybenzamine**	**Prazosin**
		Physicochemical	
Chemical	Imidazoline	Haloalkylamine	Quinazoline
Presentation	Clear sol^n 10mg/ml (mesilate)	Tablets 10mg Clear sol^n 50mg/ml (HCl)	Tablets 0.5, 1, 2, 5mg (HCl)
Route / Dose	IM: 5 – 10mg IV: infusion 0.1 – 0.2mg/min (5%D or NS)	PO: 10 – 60mg/day divided IV: infusion 10 – 40mg/hr (5%D or NS)	PO: 1mg bd – tds max 20mg daily
		Pharmacodynamics	
Use	Perioperative Mx of **phaeochromocytoma** Acute intraop HT	Pre-op Rx **phaeo** Hypertensive crisis Raynaud's	HT Raynauds AR / MR Phaeo Bladder neck obstruction
MOA	Transient competitive reversible blockade of α receptors α_1:α_2 3-5:1 Onset rapid: 1 – 2min	Covalent competitive irreversible blockade of α receptors $\alpha_1 > \alpha_2$ Slow onset (60min IV)	Highly selective competitive blockade α_1 receptors
CVS	α_1: ↓SVR 2° vasodilation → reflex ↑HR / ↑CO α_2: presynaptic inhibition → ↑NA release → + inotropy ↑CBF Class I anti-arrhythmic	α_1: ↓SVR reflex ↑HR / ↑CO ↓catecholamine induced arrhythmias	Coronary artery dilation Veno / vasodilation ↓SVR / PVR → ↓BP Min reflex ↑HR Direct neg chronotrope effect SA node ↑CO w HF
Resp	α_1: Pulmonary artery vasodilator ↑VC; ↑FEV_1; ↓histamine induced bronchoconstrict^n Nasal mucosal congestion → stuffy nose	Nasal congestion (prominent) → indicator of sufficient dose	
GIT / renal	↑salivation; ↑gastric acid prod^n; ↑motility → abdo pain	Min effect RBF	Min effect RBF / GFR Relax^n trigone / sphincter
Endocrine		↑insulin release (blocks inhibitory action of adrenaline)	↑plasma NA Min effect renin
CNS		Miosis ↓CBF (^{w}/↓BP only)	
Toxicity / SE	Orthostatic hypotension Dizziness Abdo pain / diarrhoea CV collapse / death Impotence	Orthostatic hypotension Dizziness Sedation (chronic use) Paralytic ileus Impotence	Orthostatic hypotension Dizziness Drowsiness Nausea Urinary urgency '1st dose phenomenon' = dizziness; faintness 2°

By Amanda Diaz

			↓BP, ↓HR, ↓VR
Pharmacokinetics			
Absorption	PO:20%	PO: 20 – 30%	PO: 40 – 60%
Distribution	50% protein bound	Highly lipophilic	92% protein bound (AAG) Vd 0.5 – 1L/kg
Metabolism	Extensive	Hepatic; deacetylation	Hepatic; dealkylation Active metabolites
Elimination	Urine; 10% unchanged $t_{½\beta}$: 10 – 20min	Urine & bile $t_{½\beta}$: 24hrs	Bile; <10% unchanged CL: 4ml/kg/min $t_{½\beta}$: 2.5 – 3hrs

MAKEUP: Write short notes on the pharmacology of dexmetatomidine and compare with clonidine

Properties	Dexmetatomidine	Clonidine
Physicochemical		
	Imidazole derivative	Aniline derivative
Isomerism	Purified racemic mixture → D stereoisomer is active (Dex)	No
Presentation	Solution 0.1mg/ml in NaCl Preservative free	Tablets (0.1/0.25/0.3mg) Solution 0.15mg/ml
Pharmacodynamics		
Mechanism of action	Full agonist Potent α_2 agonist, minimal α_1 activity (α_2: α_1 1600:1)	Partial agonist Less potent α_2 agonist, some α_1 activity (α_2: α_1 200:1)
	Central/spinal cord (postsynaptic) SNS (presynaptic) α_2 = G_iPCR → ↓cAMP → cell inhibition via ↑K^+ channel activity	
Uses	Sedation ventilated ICU Pts Adjunct to GA	HT Blunt surgical stimulation ↓Opioid requirements Post-op IV/regional anaes Anti-sialogogue Migraine Opiate ^{w}/drawal Chronic pain syndromes ↓Post-operative shiver
Dose	IV infusion 1µg/kg 10min → 0.2-0.7µg/kg/hr up to 24hr	PO: 0.5-0.6mg tds IV: 0.15-0.3mg tds Epidural: 0.15mg
Onset/Duration		10min / 3-7hr (IV)
Cardiovascular	Nil initial HT Prolonged ↓MAP Nil change CO/HR	Bolus: initial HT (α_1) then Prolonged ↓MAP (central α_2) Reflex ↓HR with HT (baroreceptor reflex) Nil change CO Rebounnd HT on abrupt cessation
CNS	Sedation → Pt remains cooperative and responsive while ventilated	Sedation
	Central α_2 effect	
	Anxiolytic	Anxiolytic
	Central α_2 effect	
		Analgesic
		↓ICP / ↓IOP
GIT		Anti-sialogogue ↓Intragastric P
Metabolic		↓Insulin release (small ↑BSL) ↓circulating catecholamines
Anaesthetic Implications	↓MAC, Opioid sparing	↓MAC, Opioid sparing, obtunds tourniquet HT, ↓propofol req for LMA insertion
Pharmacokinetics		
Absorption		100% oral bioavailability

By Amanda Diaz

Distribution	Vd 1.33L/kg; $t_{½\alpha}$ 6min 94% protein bound	Vd 1.7-2.5L/kg 20% protein bound
Metabolism	Extensive hepatic metabolism Glucoronidation/methylation	<50% hepatic metabolism
Elimination	95% urinary excretion $t_{½\beta}$ 2hrs; CL 39L/hr (7ml/kg/min)	65% unchanged urine 20% faeces $t_{½\beta}$ 6-23hrs CL 1.9ml/kg/min