### Physicochemistry

| Structure       | Purine nucleoside  
Purine base  
D-ribose |
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Presentation</td>
<td>IV injection 3mg/ml in NS</td>
</tr>
</tbody>
</table>

### Pharmacodynamics

#### Use
- Differentiate b/n SVT and VT  
- Treatment of SVT (90% efficacy)

#### MOA
- **↓SA & AV node activity**  
  - Activate adenosine A₁ receptors → ↑K⁺ channel opening → hyperpolarisation  
  - Antagonises cAMP-mediated catechol stimulation of vent mm (Gₛ-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; unmask AF/flutter  
  - Dose-dependent ↑myocardial BF 2° coronary aa dilatation (A₂ receptor stim³)

#### 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° A₂ 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

<table>
<thead>
<tr>
<th>Absorption/Distribution</th>
<th>IV only / Vd not measurable 2° rapid metabolism</th>
</tr>
</thead>
</table>
| Metabolism              | Absorbed into RBC → t½β 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
Describe the effects of α2 adrenoceptor agonists relevant to anaesthesia

General: α2 adrenoceptors are present on target tissues
- Presynaptically on sympathetic nerve fibres (peripheral)
- CNS / spinal cord (post-synaptic)
- Platelets

α2 adrenoceptors are GPCR
- G\textsubscript{i}-coupled adenylyl cyclase inhibition
  - Activation of receptor → ↓cAMP

Commonly used drugs:
- Clonidine
- Dexmetatomidine

Actions mediated by receptor activation:

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

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 Ca²⁺ 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: t½β 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 O₂
   - 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
     - ↓O₂ utilisation → ↑mixed venous O₂ 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
    - ↑O₂ available → supplemental O₂
    - Correct acidosis → NaHCO₃
    - ↑Sulfur donors → IV Na thiosulfate (150mg/kg over 15min)
    - ↑CN⁻ binders → hydroxycobalumin (Vit B₁₂a) → cyanocobalumin (Vit B₁₂)
    - ↑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

<table>
<thead>
<tr>
<th>Property</th>
<th>Esmolol</th>
<th>Propranolol</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Uses</strong></td>
<td>AF, atrial flutter</td>
<td>HT, angina, essential tremour, anxiety, thyrotoxicosis, HOCM, Pheo prophylaxis, migraine</td>
</tr>
<tr>
<td><strong>Physicochemical</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Presentation</td>
<td>Solution for injection (10/250mcg/ml) pH 5.5 (pain on injection)</td>
<td>Tablets (10, 40, 80, 160mg), solution for injection (1mg/ml)</td>
</tr>
<tr>
<td>Isomerism</td>
<td>Nil</td>
<td>Racemic mixture</td>
</tr>
<tr>
<td>Routes/doses</td>
<td>IV only</td>
<td>PO: 30-320mg/day (bd→tds) IV: 1-10mg</td>
</tr>
<tr>
<td><strong>Pharmacodynamics</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mechanism of Action</td>
<td>Selective β₁ block “sympathomimetic activity Peak effect 10min Off by 20min</td>
<td>Non-selective β₁/β₂ block “Sympathomimetic activity High doses inhibits Na⁺ ion flux → membrane stabiliser</td>
</tr>
<tr>
<td>CVS</td>
<td>Neg inotrope Neg chronotrope Similar ↓CO to propranolol</td>
<td>Neg inotrope Neg chronotrope ↓CO by ~20% ↓MRO₂ ↓MAP → poorly defined ?central effect</td>
</tr>
<tr>
<td>Respiratory</td>
<td>Minimal effect</td>
<td>↓FEV₁ 2° ↑airways resistance ↓ventilatory response to ↑PaCO₂</td>
</tr>
<tr>
<td>CNS</td>
<td>↓CBF 2° ↓MAP → ↓ICP</td>
<td>Cross BBB → ↓tremor, ↓IOP, anxiolytic ↓ICP, ↓vasospasm</td>
</tr>
<tr>
<td>GU</td>
<td>Nil</td>
<td>↓uterine tone</td>
</tr>
<tr>
<td>Metabolic</td>
<td>Min</td>
<td>↓renin (β₁ block JGA)→ ↓aldosterone ↓FFA ↓gluconeogenesis</td>
</tr>
<tr>
<td>Side Effects</td>
<td>Less likely to produced HF, Heart block</td>
<td>HF, heart block Bronchospasm Nightmares Mask Sx ↓BSL ↓exercise tolerance Abrupt cessation → angina, V arrhythmias, MI, sudden death</td>
</tr>
<tr>
<td>Drug interactions</td>
<td>↑recovery time from sux (5-8min)</td>
<td>Displace fentanyl from lungs</td>
</tr>
<tr>
<td><strong>Pharmacokinetics</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Absorption</td>
<td>IV only</td>
<td>90% PO Bioavailability 30% 2° 1st pass metabolism</td>
</tr>
<tr>
<td>Distribution</td>
<td>Lipid soluble (+++) 60%protein bound Vd 3.5L/kg</td>
<td>Lipid soluble (+++) 95%protein bound (AAG) Vd 3.5L/kg</td>
</tr>
<tr>
<td>Metabolism</td>
<td>Plasma hydrolysis→ red cell</td>
<td>Hepatic metabolism: oxidative</td>
</tr>
</tbody>
</table>

By Amanda Diaz
<table>
<thead>
<tr>
<th>Esterase</th>
<th>deamination → dealkylation → glucoronidation 4-hydroxy metabolite active ↓ dose in liver failure</th>
</tr>
</thead>
</table>
| Elimination | Renal: <1% unchanged CL 285ml/min/kg  
t½β 10min  
Renal disease → caution major acid metabolite renally excreted (t½β 3.5hrs)  | Renal: <1% unchanged CL 1L/min  
t½β 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 FiO₂ 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 ↓ T₄ production
  - Prevents peripheral conversion of T₄ → T₃

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Cardiovascular Drugs

- Replacement should be T₃
  - Usually reversible with cessation

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

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

Gut
- Metallic taste

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

Interactions
- 95% Protein bound
  o 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: \( \beta \) blockers are used to treat HT, pheochromocytoma, portal HT, and HF

- Mechanism of action: **Competitive** blockade of \( \beta \) adrenoceptor, preventing activation by endogenous adrenaline/NA
  - Some exhibit **partial agonist** properties (useful in HF)
- Can be **selective** for \( \beta_1 \) receptor or **non-specific** (\( \beta_1 \) and \( \beta_2 \) blockade)
- Most of the wanted effects occur with \( \beta_1 \) blockade:
  - Negative inotropy
  - Negative chronotropy
- Unwanted effects arise from \( \beta_2 \) blockade
  - \( \downarrow \)MAP 2° \( \downarrow \)CO
  - Orthostatic hypotension
- In general, **short acting \( \beta_1 \) selective blockers** are used in anaesthesia in the peri- and intra-operative period due to \( \downarrow \beta_2 \) related side-effects
  - Metoprolol
  - Esmolol

<table>
<thead>
<tr>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>↓Myocardial Work</td>
<td>↓MAP can be refractory to treat</td>
</tr>
<tr>
<td>↓O(_2) demand of heart mm</td>
<td>Unable to oppose cardiac effect of ( \beta )</td>
</tr>
<tr>
<td>2° ↓HR, ↓contractility</td>
<td>blockade</td>
</tr>
<tr>
<td>↑Diastolic time</td>
<td>Unopposed vagal tone ( \rightarrow ) eg from</td>
</tr>
<tr>
<td>↑coronary aa perfusion time ( \rightarrow )</td>
<td>peritoneal stretch, laryngoscopy is unopposed</td>
</tr>
<tr>
<td>LV perfusion ↑O(_2) supply</td>
<td>results in profound ↓MAP</td>
</tr>
<tr>
<td>↓systolic time</td>
<td>difficult to treat</td>
</tr>
<tr>
<td>2° ↑HR</td>
<td>Bradycardia</td>
</tr>
<tr>
<td>Anti-arrhythmic Effect</td>
<td>Drug Interactions</td>
</tr>
<tr>
<td>( \beta ) blockers are class II anti-arrhythmic</td>
<td>( \alpha_1 ) agonist (metaraminol) to treat ↓MAP</td>
</tr>
<tr>
<td>Stabilises myocardium</td>
<td>( \rightarrow ) ↑↑MAP ( \rightarrow ) ↑risk MI</td>
</tr>
<tr>
<td>Sotolol also class III anti-arrhythmic</td>
<td>( \text{Ca}^{2+} ) blockers ( \rightarrow ) can precipitate HF/heart block</td>
</tr>
<tr>
<td>↓MAC</td>
<td>Bradycardia</td>
</tr>
</tbody>
</table>

- Obtunds hypertensive response to Intubation Tourniquet

| Negative inotropy/chronotropy effect            |
| Precipitate CCF \( \rightarrow \) 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:
  - V₁ receptors: GPCR
    - Present in vascular smooth muscle / platelets
    - ↑ Phospholipase C → ↑ DAG / IP₃ → ↑ Ca
    - ↑ SVR, ↓ renal arteriolar vasoconstriction (efferent > afferent → maintain GFR)
  - V₂ receptors: GPCR
    - Collecting duct → ↑ aquaporin insertion into luminal membrane → ↑ H₂O absorption
    - 2° effect → ↑ urea reabsorption to ↑ osmolarity of renal medulla → ↑ H₂O movement through aquaporins
  - V₃: Anterior pituitary → ↑ ACTH release

Vasopressin:
- Synthetic nonapeptide, ADH analogue
- Administration:
  - IV for evaluation
  - DDAVP available for intranasal administration → 1° V₂ 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 V₁ and V₂ receptors
  - V₁: present in vascular smooth muscle → stimulation → vasoconstriction; most pronounced in splanchnic vasculature (↓ portal circulation) → high doses required. Renoprotective
    - Not antagonised by β blockers / denervation
  - V₂: CD and distal DCT of renal tubules → ↑ aquaporin insertion

CVS:

By Amanda Diaz
Cardiovascular Drugs

By Amanda Diaz

- ↑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

<table>
<thead>
<tr>
<th>Class</th>
<th>Mode of Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Osmotic Diuretics (mannitol)</td>
<td>Freely filtered at glomerulus, not reabsorbed → ↑osmolality of filtrate → ↓H₂O reabsorption → ↑urine vol</td>
</tr>
<tr>
<td>Use → rapid ↓ICP</td>
<td></td>
</tr>
<tr>
<td>Loop diuretics (frusemide)</td>
<td>1° action in thick ascending limb of LoH</td>
</tr>
<tr>
<td>Use CCF to ↓oedema, renal failure</td>
<td>Impair Na⁺/Cl⁻ reabsorption → impairs action of counter-current mechanism → ↓hypertonicity of medulla → ↓H₂O reabsorption in collecting duct → ↑vol urine, ↓conc urine</td>
</tr>
<tr>
<td>Thiazide diuretics (HCT)</td>
<td>1° action of early DCT, impair Na⁺ / Cl⁻ reabsorption</td>
</tr>
<tr>
<td>Use moderate HT</td>
<td>↑Na⁺ / Cl⁻ → ↑H₂O excretion</td>
</tr>
<tr>
<td></td>
<td>Late DCT → ↑Na⁺ exchange with K⁺/H⁺ → hypokalaemic hypochloremic alkalosis</td>
</tr>
<tr>
<td>Aldosterone antagonist</td>
<td>Competitive antagonist of aldosterone</td>
</tr>
<tr>
<td>(spironolactone)</td>
<td>↓K⁺ excretion (K⁺ sparing) principal cells → ↑Na⁺ / H₂O excretion</td>
</tr>
<tr>
<td>K⁺ sparing (amiloride)</td>
<td>Block Na⁺/K⁺ exchange in late DCT independent of aldosterone → ↑Na⁺ excretion, ↓K⁺ excretion, ↓H₂O reabsorption</td>
</tr>
<tr>
<td>Carbonic anhydrase inhibitors  (acetazolamide)</td>
<td>Weak diuretic only</td>
</tr>
<tr>
<td></td>
<td>Non-competitive inhibitor of CA in PCT → ↓conversion CO₂ + H₂O to H₂CO₃ then HCO₃⁻ and H⁺ → ↓Na⁺/H⁺ exchange → ↑Na⁺ /HCO₃⁻ excretion + diuresis → hyperchloraemic acidosis</td>
</tr>
<tr>
<td>Others→ not classically identified as diuretics as 1° mode of action is anti-HT</td>
<td></td>
</tr>
<tr>
<td>ACE inhibitor (-oprilis)</td>
<td>Mild K⁺ sparing effect (see above)</td>
</tr>
<tr>
<td>ATII inhibitors (-sarten)</td>
<td>Prevent conversion of ATI → ATII 1° in lungs</td>
</tr>
<tr>
<td></td>
<td>Antagonise ATII</td>
</tr>
</tbody>
</table>
2003b(6): List the potential clinical uses of α₂ adrenoceptor agonists and outline the limitation of clonidine for each

General: α₂ 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 α₂ receptor activation
- G protein coupled receptor
- Activation → ↓ adenyl cyclase activity → ↓ cAMP production

Clonidine
- partial agonist of α₂ adrenoceptor (limited α₁ activity)
- Available for oral, IV, epidural use

Clinical uses for α₂ agonists

<table>
<thead>
<tr>
<th>Use</th>
<th>Limitation of clonidine</th>
</tr>
</thead>
<tbody>
<tr>
<td>↓MAP</td>
<td>Causes transient ↑MAP (2° initial α₁ stimulation) → ↓HR (baroreceptor reflex) especially with bolus dose</td>
</tr>
<tr>
<td>Central inhibition</td>
<td>Prolonged refractory ↓MAP</td>
</tr>
<tr>
<td>↓NA release peripherally</td>
<td>Rebound ↑MAP on cessation 2° upregulation of NA with chronic use</td>
</tr>
<tr>
<td>Analgesia (neuraxial, multi-modal)</td>
<td>Analgesia 3/10 respiratory depression Synergistic w/opioid in neuraxial blockade Nil motor / sensory blockade Ceiling effect (partial agonist) Dose limited by side-effects</td>
</tr>
<tr>
<td>Dorsal horn inhibition → ↓Aδ- C-fibre afferent activity</td>
<td>Augments endogenous opiate release</td>
</tr>
<tr>
<td>Sedation (pre-med)</td>
<td>Slow-acting – unsuitable as sole sedating agent (~90min)</td>
</tr>
<tr>
<td>Central inhibition</td>
<td>Useful as ↓MAC of VA (dexmetatomidine is more selective α₂ agonist → ↓↓MAC)</td>
</tr>
<tr>
<td>Anxiolytic (pre-med)</td>
<td>Ceiling effect</td>
</tr>
<tr>
<td>Central inhibition</td>
<td>Slow-acting (~90min to peak IV) At high doses ↑anxiety</td>
</tr>
<tr>
<td>Blunt BP responses to operative stimuli (LMA insertion, tourniquet HT)</td>
<td>Relatively long-time to act (~90min IV, 3hrs PO) Ceiling effect Dose limited by side-effects</td>
</tr>
<tr>
<td>↓sympathetic outflow</td>
<td></td>
</tr>
<tr>
<td>Modulates afferent pain fibres</td>
<td></td>
</tr>
<tr>
<td>Anti-sialogogue / ↓intra-gastric P</td>
<td></td>
</tr>
<tr>
<td>↓ICP/IOP (pre-med)</td>
<td></td>
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<tr>
<td>Post-op shivering</td>
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<tr>
<td>Anti-emetic</td>
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<tr>
<td>Central inhibition</td>
<td></td>
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<tr>
<td>↓sympathetic outflow</td>
<td></td>
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<tr>
<td>↓CBF (↓MAP)</td>
<td></td>
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<tr>
<td>↓aqueous / ↓CSF production</td>
<td></td>
</tr>
<tr>
<td>Long time to peak effect</td>
<td></td>
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<tr>
<td>Long elimination t½ 9-18hrs</td>
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<tr>
<td>Partial agonism (ceiling effect)</td>
<td></td>
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<tr>
<td>Side effects</td>
<td></td>
</tr>
<tr>
<td>Large Vd (2L/kg)</td>
<td></td>
</tr>
<tr>
<td>Causes ++ dry mouth → can be useful</td>
<td></td>
</tr>
</tbody>
</table>
**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 cyclase → ↑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\(^{st}\) venodilatation
  - ↓tendency for VR
  - ↓preload RV
- Vasodilation
  - ↓end-diastolic pressure / ↓vent wall tension → ↓afterload

**Heart:**
- ↓metabolic O\(_2\) requirements
  - 2\(^{nd}\) above factors → ↓myocardial work → ↓O\(_2\) demand
- ↑coronary BF
  - 2\(^{nd}\) ↓vent wall tension (↓afterload), redirecting blood flow to subendocardium
  - 2\(^{nd}\) coronary vasodilatation → improve O\(_2\) supply
- Results in favourable ↑supply: demand ratio
- CO
  - ↓VR → ↑CO in normal Pts
    - HF Pts → ↑CO 2\(^{nd}\) ↓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\(^{nd}\) vasodilatation
    - Headache common
- Uterus
  - ↓uterine tone
  - ↑blood flow → ↑risk haemorrhage

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

By Amanda Diaz
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 (M2-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 \([\text{Ca}^{2+}]\) with action potential
  - MOA of inotropic agents → ↑[Ca\(^{2+}\)]
  - cAMP: Intracellular messenger → ↑activation intracellular proteins by activating protein kinases → ↑opening of Ca\(^{2+}\) channels → ↑[Ca\(^{2+}\)]
    - ↑cAMP production
      - Stimulation of GsPCR → ↑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 → Gs-protein activation → ↑adenyllyl 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
Cardiovascular Drugs

- inhibition by MAO in nerve terminal
  - Ephedrine

**Glucagon**
- GPCR stimulation $\rightarrow \uparrow \text{cAMP}$
- Limited use in β blocker overdose

**Histamine**
- Gs-protein stimulation $\rightarrow \uparrow \text{cAMP}$
- Nil useful cardiac role

$\downarrow \text{cAMP breakdown}$

**Phosphodiesterase (PDE) Inhibitors:**
- Aminophylline (non-specific), Milrinone (PDEIII)
- Inhibit PDE $\rightarrow \downarrow$ breakdown of cAMP (cGMP) $\rightarrow$ effective $\uparrow \text{cAMP}$

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

**Ca sensitising Agents**
- Levosimendan
  - $\uparrow$ Ca interaction with troponin C $\rightarrow$ enhance contractility without $\uparrow$ intracellular Ca
  - Activate ATP-dependent K channels on mitochondrial membrane $\rightarrow$ protect muscle from ischaemia $\rightarrow$ ischaemic preconditioning
  - ATP-dependent K channel of smooth muscle $\rightarrow$ 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 / AT1 receptor antagonist
- ↓SVR (↓angiotensin II, III) AT₁R vascular smooth muscle → ATII effect
- ↓circulating catecholamines → ATII effect
- ↑Na / H₂O excretion → ↓Aldosterone action (small ATII)
- ACE found in lung
  - Converts ATI (proprotein) → ATII (vasoconstrictor)
  - ATII → ↑aldosterone release from adrenal cortex
  - Aldosterone → ↑Na/H₂O reabsorption from DCT / CD
  - ATII may also have a direct effect on Na/H₂O 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 / H₂O reabsorption in early DCT
  - Need good renal function
- Aldosterone antagonist (Spironolactone)
  - In severe LVF
  - Weak Aldosterone competitive antagonist → ↓H₂O reabsorption CD
- K sparing diuretics (amiloride)
  - DCT blockade Na/H₂O 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

By Amanda Diaz
- 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 β₁ adrenoceptor → ↑adenyl cyclase activity → ↑cAMP → protein phosphorylation / activation protein kinases
  - Block β adrenoceptors
    - β₁ – myocardium
      - Negatively inotropic / chronotropic
        - ↓MRO₂ myocardium, improve diastolic time
        - Improves O₂ supply / demand ratio
    - β₁ – JGA
      - ↓renin release (↓activation RAA system)
  - Cardioselective β blockers (those above) have evidence to improve survival
    - Ratio of β₁ / β₂ 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 be altered by the use of MAO-I

General: Noradrenergic (NA) transmission occurs in
- postganglionic sympathetic nerve fibres excluding 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-synthesised 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 Ca²⁺ 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 (α₂ receptors)
    - Negative feedback / inhibition of further NA release by ↓Ca²⁺ influx
  - Reuptake into presynaptic neurones (major mechanism) → 1° uptake
    - 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 (MAOₐ-I) → Selegeline
- Non-selective (MAOₐ/I, MAOₐ/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
Cardiovascular Drugs

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

[Chemical diagram]
2005b(8): Describe the adverse effects of β-adrenoceptor antagonists

General: β adrenoceptors are a group of Gs protein coupled receptors
- Stimulated endogenously by: NA, adrenaline
β adrenoceptors are classified into β₁ and β₂
  - β₁: myocardial muscle cells (also JGA)
    o Stimulation: ↑adenylyl cyclase → ↑cAMP → ↑intracellular Ca²⁺
    o Stimulation results in: positive inotropy, chronotropy, dromotropy, lusitropy
    o Renal: ↑renin production → ↑ATII (constriction), ↑aldosterone (Na⁺ retention)
  - β₂: smooth muscle of blood vessels (veins, arterioles); CNS; adipose tissue; internal urethral sphincter; bronchial smooth muscle
    o Stimulation (smooth muscle): ↑adenylyl cyclase → ↑cAMP → inhibition of MLCK
    o Stimulation (elsewhere): ↑adenylyl cyclase → ↑cAMP → ↑Ca influx
    o Results in: vasodilatation, venodilatation, heightened arousal, ↑BSL, lipolysis, glycogenolysis
    o Also present on GIT, eye

β adrenoceptors antagonists inhibit the activation of the β adrenoceptor
- Uses:
  o CVS: treatment of HT, angina, peri-myocardial infarction
  o Other: Pheochromocytoma, ↑thyroidism, HOCM, Glaucoma
- All are competitive antagonists
  o Selectivity: β₁ and non-selective (β₁ β₂)
    ▪ β₂ mediates unwanted effects
    ▪ β₁ selective (cardioselective): Atenolol, esmolol, metoprolol
  o 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
  o Membrane stabilising properties
    ▪ Minimal clinical significance at therapeutic doses
- Effects:
  o Heart: Negative inotropy/ chronotropy/ dromotropy/ lusitropy, ↓SA node automaticity, ↓AV node conduction
    ▪ ↑CorP time → ↑O₂ supply to myocardium
    ▪ ↓MRO₂
    ▪ In Pt with LVF → may precipitate HF (rare for the selective β₁ antagonists and partial agonists) as ↓CO
    ▪ Inappropriate bradycardia, orthostatic hypotension (↑with ↓blood vol)
  o Class 2 anti-arrhythmic
    ▪ Useful in AF
    ▪ Sotolol can produce unwanted arrhythmia (torsades de pointes)

By Amanda Diaz
o Circulation: Overall ↓MAP
  ▪ ↓HR → ↓CO
  ▪ β₁ blockade at JGA → ↓RAA → ↓vasoconstriction, ↓aldosterone production
  ▪ Presynaptic β₂ blockade → ↓NA release
  ▪ In elderly → may cause orthostatic hypotension
  ▪ In anaesthesia → refractory hypotension, ↓effectiveness of vasopressors
  ▪ In anaesthesia → refractory hypotension, ↓effectiveness of vasopressors

o Respiratory: Bronchoconstriction/spasm (β₂ blockade)
  ▪ ↑in asthmatics
  ▪ Can ↑sensitivity of airway to instrumentation

o 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

o CNS: Lipid soluble agents (propranolol, metoprolol)
  ▪ Anxiolytic
  ▪ May cause: depression, hallucinations, nightmares, paranoia, fatigue
  ▪ ↓IOP → good for glaucoma

o GIT:
  ▪ Dry mouth, GI disturbance

o 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 O₂
- ↑FiO₂ → ↑alveolar O₂ in areas undergoing gas exchange
- Adverse effects:
  o Removal of hypoxic pulmonary vasoconstriction to non-ventilated units → ↑shunt → ↓O₂ content of blood

Adrenaline: Non-specific α/β adrenoceptor agonist
- Route: Nebulised (direct airways, ↓systemic effects); IM; IV
- Dose: 1mg neb; 1mg IMI
- MOA:
  o β₂ agonist effect: G,PCR → ↑adenyl cyclase → ↑cAMP → ↓Ca
    ▪ ↓bronchial smooth muscle tone → ↓airways resistance
    ▪ ↓mucous production → ↓airways resistance
- Adverse Effects: 2° α/β agonist effects systemically
  o α₁: peripheral vasoconstriction → ↑BP; cutaneous constriction (pallour); difficulty with obtaining venous access
  o β₁: ↑HR, precipitate arrhythmias
    ▪ ↑MRO₂ → ischaemia
  o Nausea, abdominal pain
  o ↓insulin → ↑BSL

Salbutamol: Selective β agonist (β₂ > β₁)
- Route: Nebulised
- Dose: 5mg neb
- MOA:
  o Non-selective β agonist, nebulised further ↓systemic effects
  o GPCR → ↑adenyl cyclase → ↑cAMP → ↓Ca
    ▪ ↓bronchial smooth muscle tone
    ▪ ↓secretions
- Adverse Effects: related to systemic β agonist effects
  o β₁: ↑HR; palpitations
  o β₂: stimulation of skeletal muscle → tremour
    ▪ sweating
    ▪ postural hypotension (vasodilator)
  o Removal of hypoxic pulmonary vasoconstriction → needs supplemental O₂
  o ↓K⁺ by ↑intracellular shift
  o N&V
  o ↑BSL

By Amanda Diaz
**Ipratropium Bromide**: Anticholinergic (Atrovent)
- **Route**: Nebulised
- **Dose**: 500μg
- **MOA**: Competitive inhibition of mAChR (M3) on bronchial smooth muscle
  → GPCR → blockade → ↓phospholipase C → ↓DAG, IP3 ↓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 A2 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 → ↓TXA2) → ↑bleeding

**Methylxanthines**: Theophylline / aminophylline
- **Route**: IV / PO / PR
- **Dose**:
  - PO: 900mg divided doses
  - IV 5mg/kg bolus; infusion 0.5mh/kg/hr
- **MOA**: Phosphodiesterase 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 O₂
  - 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:
  o Minimal if in the course of anaesthetic
  o ↑fraction → ↓BP

*Helium (Heliox)*
- MOA: Lower density (and specific gravity) than air / O₂
  o During turbulent flow → ↑velocity cf O₂
  o ↓work of breathing
  o Improves oxygenation
- Adverse Effects:
  o Minimal
  o Needs to be on machine
  o ↓inspired O₂ cf O₂ alone

*Magnesium*
- Route IV
- Dose: 20mmol
- MOA: Smooth muscle relaxation → Ca channel blockade → ↓Ca
  o ↓neutrophilic burst rate → ↓inflammatory mediator release
- Adverse Effects:
  o Sedation
  o 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
  o Blocks transmission of:
    - Sympathetic B fibres (small unmyelinated post-ganglionic fibres)
    - Aδ- and C-fibres +/- motor blockade
  o Level of blockade is dose-dependent
- Removal of SNS stimulation will result in:
  o Heart (high block ~T1-4): ↓chronotropy, ↓dromotropy, ↓inotropy, ↓lusitropy
    - ↓SV → ↓CO
  o 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
  o Direct stimulation of adrenoceptors
  o Indirect stimulation of adrenoceptors via ↑NA release
    - All non-endogenous sympathomimetics have this effect >> ephedrine

<table>
<thead>
<tr>
<th>Action</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mixed α/β agonists:</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>↑TPR (vasoconstrict) α₁ effect</td>
<td>Low dose infusion→ β effects</td>
<td>↓MAP 2° β₂ stimulation (↓TPR)</td>
</tr>
<tr>
<td>↑VR (venoconstrict) α₁ effect</td>
<td>1° → ↑CO, ↑corP</td>
<td>Need CVC for infusion</td>
</tr>
<tr>
<td>↑CO (↑HR, contractility, SV) β₁ effect</td>
<td>High dose/bolus → α₁, 1° → ↑TPR/↑VR → useful in arrest</td>
<td>Must be diluted</td>
</tr>
<tr>
<td>Adrenaline</td>
<td>Short acting</td>
<td></td>
</tr>
<tr>
<td>Direct α/β stim</td>
<td>No tachyphylaxis</td>
<td></td>
</tr>
<tr>
<td>Ephedrine</td>
<td>Easy to draw up (1:10)</td>
<td>Tachyphylaxis (NA depletion in terminals)</td>
</tr>
<tr>
<td>Direct α/β</td>
<td>Rapid onset (1-2min)</td>
<td>Arrhythmogenic</td>
</tr>
<tr>
<td>Indirect ↑NA release</td>
<td>Not metabolised by MAO/COMT</td>
<td>Renal dependent excretion</td>
</tr>
<tr>
<td>1. Eph transported to nn terminal thru uptake 1 → displace NA from vesicles into cytosol → some degraded by MAO, rest release via carrier-mediated diffusion into cleft (Ca-independent as not exocytosis)</td>
<td>Relatively long duration of action (t½β₂ 4hrs)</td>
<td>Peripheral IVC OK</td>
</tr>
<tr>
<td>Nil effect uterine BF</td>
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<td></td>
</tr>
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</table>
### Dopamine

<table>
<thead>
<tr>
<th></th>
<th>Low dose infusion</th>
<th>Infusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Direct α/β</td>
<td>→ β₁, 1° → ↑CO, ↑CorP</td>
<td>Difficult titratability b/n low (&lt;10mcg/kg/min) and high (&gt;10mcg/kg/min)</td>
</tr>
<tr>
<td>Indirect ↑NA release</td>
<td>→ ↑NA release</td>
<td>Interact MAOI</td>
</tr>
<tr>
<td></td>
<td>High infusion → α 1° → ↑TPR / ↑VR</td>
<td>Need CVC</td>
</tr>
<tr>
<td></td>
<td>↓Arrhythmogenicity of adrenaline</td>
<td>Short acting (10min)</td>
</tr>
</tbody>
</table>

### α₁ agonists

- Peripheral vasoconstriction → ↑TPR → ↑MAP
- ↑VR (venoconstriction)

<table>
<thead>
<tr>
<th>NA (α₁, min β)</th>
<th>Duration action 30-40min ↑CorP</th>
<th>Reflex ↓HR 2° baroreceptor reflex → ↓CO</th>
</tr>
</thead>
<tbody>
<tr>
<td>↑TPR / ↑VR</td>
<td></td>
<td>Rapidly metabolised (MAO/COMT) Arrhythmogenic</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Metaraminol (1° α₁, min β)</th>
<th>1:20 dilution</th>
<th>Reflex ↓HR 2° baroreceptor reflex → ↓CO</th>
</tr>
</thead>
<tbody>
<tr>
<td>Direct/indirect ↑TPR</td>
<td>Rapid onset (1-2min) Relatively long action (1hr)</td>
<td>Rapid ↑MAP → LVF in susceptible Pts</td>
</tr>
<tr>
<td></td>
<td>↑coronary BF (indirect) Nil effect uterine BF</td>
<td></td>
</tr>
</tbody>
</table>

### Phenylephrine

- Nil β effect
- Not arrhythmogenic

### β₁ 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 & O₂

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
  o Biphasic 200J
  o Monophasic 360J
- Aim: Terminate irregular rhythm

Drug Therapy

Adrenaline → 1ˢᵗ line drug
- 1mg, repeated every 3 minutes
MOA: α / β agonist → 1ˢᵗ action in arrest
  - α₁: GPCR → ↑phospholipase C → ↑DAG, IP₃, Ca²⁺
    o ↑SVR 2ˢᵗ vasoconstriction
    o ↑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 2ˢᵗ ↑K⁺ channel opening
  - Class 1 properties → ↓opening fast Na channels
  - Class 4 properties → ↓opening Ca channels (↓plateau)
Adverse Effects
- AV node block → 3ˢᵗ 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 V₁ receptors ↑phospholipase C → peripheral vasoconstriction

By Amanda Diaz
Adverse Effects: Coronary artery vasoconstriction

NaHCO₃
MOA: Reverse acidosis (metabolic acidosis 2° ↑ anaerobic metabolism)
- Correct ↓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/H₂O 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
  o Active drug metabolised to active metabolites → captopril
  o Prodrugs activated by hepatic metabolism → ramipril
  o Active drug excreted unchanged in urine → lisinopril
- MOA: prevent conversion ATI → ATII (and less potent ATIII)
  o ↓aldosterone release
  o ↓ peripheral vasoconstriction
- Use:
  o HT & CCF
  o ↓mortality in HF assoc with MI 2° ↓cardiac remodelling
- Side effects:
  o Prevents breakdown of kinins (eg bradykinin)
    • Persistent cough
    • Angioedema
  o Rash
  o Headache
  o ↑K
  o ↑renin levels (ATII acts part of negative feedback inhibition)
- Drug interactions:
  o NSAIDs → critical ↓renal afferent arteriole → precipitate renal failure
  o ↑↑K with K-sparing diuretics

Angiotensin II receptor antagonist (irbesarten)
- MOA: competitively inhibit AT₁ receptor
  o Adrenal cortex → ↓aldosterone release
  o Peripheral vessels → prevent vasoconstriction
  o Some direct ATII receptors on DCT/CD
- Use:
  o As with ACEI
  o ↑renin (2° blocking ATII negative feedback) → ↑↑ATII levels
  o Better tolerated in those with kinin related S/E → cough, angioedema
- AT₂R remains unblocked
  o 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 stabilisers**

**Class 1a: Procainamide; 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 dysrhythmias)
- Effect on AP:
  - Little effect phase 0
  - ↓height of spike
  - ↓duration AP
  - Shortens refractory period

**Class 1c: Flecainide**
- Membrane stabilisers → suppress re-entrant rhythms
Cardiovascular Drugs

- Effect on AP:
  - ↓phase 0 depolarisation
  - Nil effect duration AP → \(\delta\)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

<table>
<thead>
<tr>
<th></th>
<th>pH</th>
<th>Osmolarity</th>
<th>Electrolytes</th>
<th>Sugar</th>
<th>Elimination</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Saline Solutions</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.9%</td>
<td>4.5 – 7</td>
<td>304 mOsm</td>
<td>Na 150</td>
<td>Cl 150</td>
<td>0</td>
</tr>
<tr>
<td>3%</td>
<td>5.6</td>
<td>1000 mOsm</td>
<td>Na 500</td>
<td>Cl 500</td>
<td>0</td>
</tr>
<tr>
<td>7.5%</td>
<td>5.6</td>
<td>2567 mOsm</td>
<td>Na 1283</td>
<td>Cl 1283</td>
<td>0</td>
</tr>
<tr>
<td><strong>Dextrose Solutions</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5%</td>
<td>4</td>
<td>252 mOsm</td>
<td>0</td>
<td>50g/L Glucose</td>
<td>t½β 30min</td>
</tr>
<tr>
<td>4%D 1/5NS</td>
<td>310 mOsm</td>
<td>Na 30</td>
<td>Cl 30</td>
<td>40g/L Glucose</td>
<td>t½β 30min</td>
</tr>
<tr>
<td><strong>Hartmann’s (CSL)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5 – 7</td>
<td>274 mOsm</td>
<td>Na 129</td>
<td>Cl 109</td>
<td>0</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>K 5</td>
<td>Ca 2</td>
<td>Lactate 29</td>
</tr>
<tr>
<td><strong>Mannitol</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>20%</td>
<td>5 – 7</td>
<td>1098 mOsm</td>
<td>Na 140</td>
<td>Cl 128</td>
<td>0</td>
</tr>
<tr>
<td><strong>Albumin</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4% (50g/L)</td>
<td>290 mOsm</td>
<td>Na 140</td>
<td>Cl 128</td>
<td>0</td>
<td>t½β 72min</td>
</tr>
<tr>
<td>20% (250g/L)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Dextran (fermenter sucrose)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>70</td>
<td>300 mOsm</td>
<td>Na 150</td>
<td>Cl 150</td>
<td>t½β 6hrs</td>
<td></td>
</tr>
<tr>
<td>40 (anaphylaxis 1:3000)</td>
<td>300 mOsm</td>
<td>Na 150</td>
<td>Cl 150</td>
<td>t½β 2hrs</td>
<td></td>
</tr>
<tr>
<td><strong>Synthetic Colloids</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gelofusin MW 30kDa</td>
<td>7.4</td>
<td>274 mOsm</td>
<td>Na 154</td>
<td>Cl 120</td>
<td>t½β 3hrs</td>
</tr>
<tr>
<td>Haemocell MW 35kDa</td>
<td>7.3</td>
<td>301 mOsm</td>
<td>Na 154</td>
<td>Cl 154</td>
<td>t½β 3hrs</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>K 5.1</td>
<td>Ca 6.25</td>
<td></td>
</tr>
</tbody>
</table>

- Anaphylaxis: 1:1000
- Excreted renal (80%); bile (10%)
- Care with blood transfusions (citrated blood) → Ca will ↑ clotting
MAKEUP: Discuss the pharmacology of \( \alpha_1 \) antagonists. Compare and contrast phentolamine, phenoxybenzamine and prazosin

General: \( \alpha \)-adrenergic antagonists bind selectively to \( \alpha \)-adrenergic receptors
- prevent activation by catecholamines
  - cardiac and peripheral vasculature

<table>
<thead>
<tr>
<th></th>
<th>Phentolamine</th>
<th>Phenoxybenzamine</th>
<th>Prazosin</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Chemical</strong></td>
<td>Imidazoline</td>
<td>Haloalkylamine</td>
<td>Quinazoline</td>
</tr>
<tr>
<td><strong>Presentation</strong></td>
<td>Clear sol(^n) 10mg/ml (mesilate)</td>
<td>Tablets 10mg Clear sol(^n) 50mg/ml (HCl)</td>
<td>Tablets 0.5, 1, 2, 5mg (HCl)</td>
</tr>
<tr>
<td><strong>Route / Dose</strong></td>
<td>IM: 5 – 10mg IV: infusion 0.1 – 0.2mg/min (5%D or NS)</td>
<td>PO: 10 – 60mg/day divided IV: infusion 10 – 40mg/hr (5%D or NS)</td>
<td>PO: 1mg bd – tds max 20mg daily</td>
</tr>
</tbody>
</table>

**Pharmacodynamics**

<table>
<thead>
<tr>
<th>Use</th>
<th>Perioperative Mx of <strong>phaeochromocytoma</strong> Acute intraop HT</th>
<th>Pre-op Rx <strong>phaeo</strong> Hypertensive crisis Raynaud's</th>
<th>HT Raynauds AR / MR Phaeo Bladder neck obstruction</th>
</tr>
</thead>
<tbody>
<tr>
<td>MOA</td>
<td>Transient competitive reversible blockade of ( \alpha ) receptors ( \alpha_1: \alpha_2 ) 3-5:1 Onset rapid: 1 – 2min</td>
<td>Covalent competitive irreversible blockade of ( \alpha ) receptors ( \alpha_1 &gt; \alpha_2 ) Slow onset (60min IV)</td>
<td>Highly selective competitive blockade ( \alpha_1 ) receptors</td>
</tr>
<tr>
<td>CVS</td>
<td>( \alpha_1: \downarrow SVR ) ( \uparrow ) vasodilation ( \uparrow ) reflex ( \uparrow ) HR / ( \uparrow ) CO ( \alpha_2: ) presynaptic inhibition ( \uparrow ) NA release ( \uparrow ) inotropy ( \uparrow ) CBF Class I anti-arrhythmic</td>
<td>( \alpha_1: \downarrow SVR ) reflex ( \uparrow ) HR / ( \uparrow ) CO ( \downarrow ) catecholamine induced arrhythmias</td>
<td>Coronary artery dilation Veno / vasodilation ( \downarrow ) SVR / PVR ( \downarrow ) BP Min reflex ( \uparrow ) HR Direct neg chronotrope effect SA node ( \uparrow ) CO w HF</td>
</tr>
<tr>
<td>Resp</td>
<td>( \alpha_1: ) Pulmonary artery vasodilator ( \uparrow ) VC; ( \uparrow ) FEV; ( \downarrow ) histamine induced bronchoconstrict ( \downarrow ) Nasal mucosal congestion ( \rightarrow ) stuffy nose</td>
<td>Nasal congestion (prominent) ( \rightarrow ) indicator of sufficient dose</td>
<td>Min effect RBF Relax(^n) trigone / sphincter</td>
</tr>
<tr>
<td>GIT / renal</td>
<td>( \uparrow ) salivation; ( \uparrow ) gastric acid prod(^n); ( \uparrow ) motility ( \rightarrow ) abdo pain</td>
<td>Min effect RBF</td>
<td>( \uparrow ) plasma NA Min effect renin</td>
</tr>
<tr>
<td>Endocrine</td>
<td>( \uparrow ) insulin release (blocks inhibitory action of adrenaline)</td>
<td>( \uparrow ) plasma NA Min effect renin</td>
<td></td>
</tr>
<tr>
<td>CNS</td>
<td>Miosis ( \uparrow ) CBF (^n) ( \downarrow ) BP only</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Toxicity / SE</td>
<td>Orthostatic hypotension Dizziness Abdo pain / diarrhoea CV collapse / death Impotence</td>
<td>Orthostatic hypotension Dizziness Sedation (chronic use) Paralytic ileus Impotence</td>
<td>Orthostatic hypotension Dizziness Drowsiness Nausea Urinary urgency ‘1(^{st}) dose phenomenon’ = dizziness; faintness 2°</td>
</tr>
</tbody>
</table>

By Amanda Diaz
<table>
<thead>
<tr>
<th>Pharmacokinetics</th>
<th>↓BP, ↓HR, ↓VR</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Absorption</strong></td>
<td>PO: 20%</td>
</tr>
<tr>
<td><strong>Distribution</strong></td>
<td>50% protein bound</td>
</tr>
<tr>
<td><strong>Metabolism</strong></td>
<td>Extensive</td>
</tr>
<tr>
<td><strong>Elimination</strong></td>
<td>Urine; 10% unchanged</td>
</tr>
<tr>
<td>t½β: 10 – 20min</td>
<td>t½β: 24hrs</td>
</tr>
</tbody>
</table>
MAKEUP: Write short notes on the pharmacology of dexmetatamidine and compare with clonidine

<table>
<thead>
<tr>
<th>Properties</th>
<th>Dexmetatamidine</th>
<th>Clonidine</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Physicochemical</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Isomerism</td>
<td>Purified racemic mixture → D sterioisomer is active (Dex)</td>
<td>No</td>
</tr>
<tr>
<td>Presentation</td>
<td>Solution 0.1mg/ml in NaCl Preservative free</td>
<td>Tablets (0.1/0.25/0.3mg) Solution 0.15mg/ml</td>
</tr>
<tr>
<td><strong>Pharmacodynamics</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mechanism of action</td>
<td>Full agonist Potent $\alpha_2$ agonist, minimal $\alpha_1$ activity ($\alpha_2$: $\alpha_1$ 1600:1)</td>
<td>Partial agonist Less potent $\alpha_2$ agonist, some $\alpha_1$ activity ($\alpha_2$: $\alpha_1$ 200:1)</td>
</tr>
<tr>
<td>Uses</td>
<td>Sedation ventilated ICU Pts Adjunct to GA</td>
<td>HT Blunt surgical stimulation ↓Opioid requirements Post-op IV/regional anaes Anti-sialogogue Migraine Opiate withdrawal Chronic pain syndromes ↓Post-operative shiver</td>
</tr>
<tr>
<td>Dose</td>
<td>IV infusion 1µg/kg 10min → 0.2-0.7µg/kg/hr up to 24hr</td>
<td>PO: 0.5-0.6mg tds IV: 0.15-0.3mg tds Epidural: 0.15mg</td>
</tr>
<tr>
<td>Onset/Duration</td>
<td>10min / 3-7hr (IV)</td>
<td></td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>Nil initial HT Prolonged ↓MAP Nil change CO/HR</td>
<td>Bolus: initial HT ($\alpha_1$) then Prolonged ↓MAP (central $\alpha_2$) Reflex ↓HR with HT (baroreceptor reflex) Nil change CO Rebounded HT on abrupt cessation</td>
</tr>
<tr>
<td>CNS</td>
<td>Sedation → Pt remains cooperative and responsive while ventilated</td>
<td>Sedation Central $\alpha_2$ effect Anxiolytic Central $\alpha_2$ effect Analgesic ↓ICP / ↓IOP</td>
</tr>
<tr>
<td>GIT</td>
<td>Anti-sialogogue ↓Intragastric P</td>
<td></td>
</tr>
<tr>
<td>Metabolic</td>
<td>↓Insulin release (small ↑BSL) ↓circuiting catecholamines</td>
<td></td>
</tr>
<tr>
<td>Anaesthetic Implications</td>
<td>↓MAC, Opioid sparing</td>
<td>↑MAC, Opioid sparing, obtunds tourniquet HT, ↓propofol req for LMA insertion</td>
</tr>
<tr>
<td>Pharmacokinetics</td>
<td>100% oral bioavailability</td>
<td></td>
</tr>
</tbody>
</table>

By Amanda Diaz
| Distribution | Vd 1.33L/kg;  
| t½α 6min  
| 94% protein bound | Vd 1.7-2.5L/kg  
| 20% protein bound |
| Metabolism | Extensive hepatic metabolism  
| Glucuronidation/methylation | <50% hepatic metabolism |
| Elimination | 95% urinary excretion  
| t½β 2hrs;  
| CL 39L/hr (7ml/kg/min) | 65% unchanged urine  
| 20% faeces  
| t½β 6-23hrs  
| CL 1.9ml/kg/min |