**Primary Cast Episode 8 - Cardiovascular Pharmacology**

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1. **Sodium channel blockers**
   **Lignocaine**
   **Describe the MOA of lignocaine on the heart**
   - Class IB antiarrhythmic drug
   - Blocks activated and inactivated Na channels
   - Greater effects on cells with longer action potentials i.e. ventricular and purkinje fibres.
   - Does not prolong the action potential

   **What are the adverse effects of lignocaine?**
   CNS: dizziness, anorexia, nausea vomiting, tinnitus, slurred speech, paresthesias
   CVS: bradycardia, cardiovascular collapse, hypotension
   Allergy

   **Flecainide**
   **What is the mechanism of action of flecainide?**
   - Class IC antiarrhythmic drug
   - Na channel blockade
   - Inhibits the fast upstroke of the action potential
   - Minimal effect on the action potential duration

   **What are the pharmacokinetics of flecainide?**
   - Well absorbed orally
   - Half life 20 hours
   - Peak plasma levels at 3 hours
   - 30% excreted unchanged
   - The rest metabolised by the liver

   **In which patients is it contraindicated?**
   Those with hypotension and LV dysfunction

2. **Beta Blockers**
   **Propranolol**
   **Describe the pharmacodynamics and clinical effects of propranolol**
   - Beta blocker - competitive, non selective blocker at B1 and B2 receptors
   - CVS: decreases BP and HR, negatively chronotropic and inoptropic. Decreases the effect of catecholamines.
   - Inhibits the peripheral conversion of T4 to T3 making it useful in thyrotoxicosis
   - Propranolol also has some activity as a sodium channel blocker

**What are the adverse effects of propranolol?**

- CVS: bradycardia, hypotension, worsening of CCF, QRS widening, arrhythmias in toxicity
- CNS: sedation, depression, abnormal dreams, depression
- Resp: worsening asthma/COPD
- Decreased exercise tolerance, decreased libido, can mask symptoms of hypoglycaemia

**Metoprolol**

**Describe the pharmacokinetics of metoprolol**

- Given oral or IV
- Well absorbed, but bioavailability is 50% due to 1st pass effect (usually give half the dose IV)
- Large Vd
- Half life 3-4 hours so BD dosing
- Liver metabolism

**How is metoprolol different from propranolol?**

- Metoprolol is B1 specific and propranolol is not
- Metoprolol has no action on sodium channels

**Sotalol**

**Describe the pharmacodynamics of sotalol**

- Non selective beta blocker, class II
- Also has Class III action, prolongs the plateau phase

**What are the main side effects of sotalol?**

- Proarrhythmic - especially QTc prolongation and torsades
- Can exacerbate CCF and asthma
- Can cause AV blockade

**What drugs interact with sotalol to prolong the QT?**

- Other drugs which prolong QTc = phenothiazines, such as chlorpromazine
- Macrolide antibiotics -azithromycin, erythromycin
- Some antidepressants, such as amitriptyline
- Drugs which cause hypokalaemia - like frusemide and other diuretics
- Drugs which depress the myocardium
- Calcium channel blockers that can increase refractory time

3. **Amiodarone**

**What antiarrhythmic class does amiodarone belong to?**

Class III, but also has effects from class I, II and IV.

**What are the effects of amiodarone on the heart?**

- Increases the action potential duration due to blockade of K current
- Prolongs the QT interval
- Also blocks inactivated Na channels
- Weak adrenergic and Ca channel blocker
- Decreases automaticity

**In what arrhythmias is amiodarone used?**

- Atrial and ventricular tachyarrhythmias, such as
- Atrial fibrillation
- Ventricular tachycardia
- Ventricular fibrillation
- SVT (re-entrant or accessory)

**What acute and chronic adverse effects can amiodarone cause?**

Acute

- Arrhythmias: Bradycardia, heart block, torsades (rarely)
- Hypotension

Chronic

- Pulmonary fibrosis
- Abnormal LFTs and hepatitis
- Skin deposits leading to photodermatitis and grey-blue discolouration
- Corneal microdeposits
- Hypo or hyperthyroidism in both acute and chronic

**What are some important drug interactions with amiodarone?**

- Warfarin - increased anticoagulant effect via decreased warfarin metabolism
- Digoxin - risk of digoxin toxicity by increasing the plasma concentration
- Increased cardiac effects of other antiarrhythmic medications due to overlapping MOAs (procainamide, flecainide, beta blockers)
- Increases the plasma concentration of phenytoin

## 4. Calcium channel blockers

**Describe the MOA of calcium channel blockers**

- Blocks voltage gated Ca channels
- Reduces the frequency of opening when depolarised
- Resulting in decreased calcium current, decreased calcium influx
- Causes vascular smooth muscle relaxation (therefore reducing afterload) - this effect is greater in dihydropyridines
- Effects on the heart include decreased SA firing, decreased AV nodal conduction, decreased contractility and cardiac output

- Verapamil and diltiazem also have a non specific anti-adrenergic effect

**What are the toxic effects of calcium channel blockers?**

- Minor: flushing, dizziness, nausea, constipation, peripheral oedema
- CVS - bradycardia, AV block, hypotension, heart failure, cardiac arrest

**What are the indications for verapamil?**

Angina, hypertension, atrial arrhythmias

**What medications can be used to treat verapamil toxicity?**

- IV calcium
- High does insulin euglycaemic therapy

5. **Adenosine**

**What is adenosine and how does it work?**

- A naturally occurring nucleoside
- Blocks the AV conduction by hyperpolarising the AV node, causes increased refractory period
- Does this by activating inward rectifying K channels and suppression of calcium dependent action potentials
- This interrupts the re-entry pathway through the AV node

**What are the indications?**

Conversion of paroxysmal SVT to sinus rhythm

**What are the pharmacokinetics?**

- Short half life of around 10 secs, duration of action 30 seconds
- Metabolised rapidly by adenosine deaminase in endothelial and red cells
- Must be given by rapid IV bolus through a proximal cannula with a good flush

**What are the adverse effects?**

Chest tightness, dyspnoea, flushing, headache, nausea, hypotension, bronchospasm, sense of impending doom, high grade AV block.

**What are the potential interactions?**

- Theophylline inhibits effects as it is an adenosine receptor blocker
- Dipyridamole enhances the effects as it is an adenosine uptake blocker
- Interacts with other AV nodal blocking drugs to increase the effects

6. **Digoxin**

Describe the pharmacodynamics of digoxin

- Inhibitor of Na/K ATPase
    - Increases intracellular Na and decreases intracellular K

    - Increased intracellular Na leads to reduced Na/Ca echanger activity, which leads to an increase in intracellular calcium
    - Increased intracellular calcium causes increased contractility
    - Inhibition of the na/K ATPase in vascular smooth muscle causes depolarisation, causing smooth muscle contraction and vasoconstriction
- Electrical effects - shortening of action potential due to shortened atrial and ventricular refractoriness. Note: this can cause increased automaticity of the heart leading ro bigeminy, VT and VF
- Parasympathetic and sympathetic effects
    - Low doses = parasympathetic - bradycardia and AV node block (early signs of toxicity)
    - Higher doses = increased sympathetic effects which can further senstise the myocardium to automaticity and increase risk of arrhythmias

**What are the non cardiac signs of digoxin toxicity**

- GIT: anorexia, nausea, vomiting, diarrhoea
- CNS: disorientation, hallucinations, yellow/green vision, centrally mediated nausea via action on the chemoreceptor trigger zone (CTZ)

**Why are patients in heart failure prone to digoxin toxicity?**

- Poor renal function due to low cardiac output
- Dehydration and other drug interactions such as diuretics, antihypertensives and calcium channel blockers
- Fluid distribution changes in heart failure, including electrolyte abnormalities

**What factors may predispose to digoxin toxicity**

- Electrolyte imbalance
    - Hypokalaemia (K inhibits digoxin bindings to the Na/K ATPase)
    - Hypercalcaemia (potentiates digoxin toxicity by increasing intracellular Ca stores, which promotes automaticity)
- Drugs that increase digoxin effect Amiodarone (by increasing plasma digoxin concentration)
    - Diltiazem, Verapamil
    - Macrolide antibiotics
    - K depleting drugs including diuretics
- Organ disease
    - renal failure (because of the PK)
    - Hypothyroidism

**Antihypertensives**

7. **ACE inhibitors & Angiotensin receptor blockers**

   **What is the mechanism of action of ramipril?**

   ACE inhibitors cause a reduction in systemic BP due to the following mechanisms

- Inhibits angiotensin converting enzyme from hydrolyzing angiotensin I to angiotensin II
- Angiotensin II is a vasoconstrictor hence its reduction results in a decrease in vascular tone (main effect)
- Angiotensin II leads to aldosterone secretion, hence its reduction leads to reduced Na and H2o retention, leading to a reduced BP
- Angiotensin II metabolises bradykinin to its inactive form. Its reduction results in an increase in bradykinin, leading to vasodilation and a further reduction in BP

How is it eliminated and why is this important
Eliminated primarily by the kidneys so doses should be reduced in patients with renal insufficiency

**What are the clinical uses of ACE inhibitors?**

- Congestive heart failure after MI, helps preserve LV function and reduce post MI remodelling
- Diabetic nephropathy - reduces proteinuria, improves intrarenal haemodynamics
- Hypertension

**What are the adverse effects of ramipril?**

- Severe first dose hypotension - especially in fluid depleted patients
- Acute renal failure - especially in those with renal artery stenosis or a solitary kidney
- Hyperkalaemia
- Angioedema
- Others: Dizziness, headache, weakness, loss of taste, diarrhoea, rash, fever, joint pain, wheezing, teratogenic or foetal abnormalities

**What adverse drug interactions may occur with ACE inhibitors?**

- Diuretics and antihypertensives → hypotension
- General anaesthetics → hypotension
- Lithium → lithium toxicity from increased resorption
- NSAIDs → hyperkalaemia and reduced activity of ACE inhibitor via blockage of bradykinin
- K sparing diuretics or K supplements → hyperkalaemia

**What advantages to angiotensin receptor blockers have over ACE inhibitors?**
No effect on bradykinin so reduced incidence of cough and angioedema
More complete inhibition of actions of angiotensin II

**ARBs**
**Describe the MOA of irbesartan**

- Competitive selective antagonist of angiotensin receptor (AT1)
- Causes vasodilation, inhibition of aldosterone secretion

**What are specific contraindications to ARBs?**

- Non-diabetic renal failure
- Pregnancy
- Allergy or previous reaction
- Hyperkalaemia
- Renal artery stenosis

8. **Prazosin**

**What is the MOA of prazosin?**

- Selectively blocks alpha-1 receptors in arterioles and venules
- Reduces arterial pressure by dilating both resistance and capacitance vessels
- A1 receptor selectivity allows noradrenaline to exert unopposed negative feedback (mediated by presynaptic a2 receptors) on its own release

**What are the side effects of prazosin?**

- Postural hypotension/syncope
- Reflex tachycardia, palpitations
- Headache
- Lassitude
- Reduced prostate smooth muscle tone, thus alleviating prostatic urinary obstruction
- Alteration to triglycerides and cholesterol levels

9. **Frusemide**

**What is the mechanism of action of frusemide?**

- Loop diuretic
- Actively secreted into the lumen from proximal tubule
- Selectively inhibits Na/K/2Cl cotransporter in the thick ascending limb of loop of Henle
- Prevents reabsorption of Na and Cl
- Abolishes the counter current mechanism leading to large volumes of dilute urine

**What are the pharmacokinetics?**

- Well absorbed, variable PO bioavailability from 10-100%
- Onset post oral is 1-3 hours, post IV is 15-30 mins
- Duration post oral is 2-6 hours (i.e. lasix, lasts six) post IV is 2 hours
- Highly albumin bound
- Small amount of hepatic metabolism but mostly renal elimination

**What are the adverse effects?**

- Related to hypovolemia- orthostatic hypotension, dehydration
- Electrolyte abnormalities: hyponatraemia, hypokalaemia, hypomagnesemia, metabolic alkalosis

- Ototoxicity, tinnitus, vertigo
- GIT: pancreatitis, jaundice, nausea/vomiting
- Raised uric acid causing gout
- Thrombocytopaenia
- Rash and other hypersensitivity reactions

**What are the possible drug interactions?**

- NSAIDs and aminoglycosides causing renal injury
- Digoxin - causing dig toxicity
- Lithium - loop diuretics increase the clearance of lithium
- Other diuretics - hypovolaemia

**10. Thiazides**

**What is the MOA of thiazides?**

Inhibition of Na/Cl transporter in the DCT leading to increased NaCl excretion and diouresis

**What are the clinical indications for thiazide diuretics**

- HTN
- Heart Failure
- Nephrolithiasis
- Nephrogenic diabetes insipidus
- Generalised oedema
- Nephrotic syndrome
- Cirrhosis

**What are the potential adverse effects of thiazide diuretics?**

- Hypokalaemia
- Dehydration, postural hypotension, hypovolaemia
- Hyponatremia
- Metabolic alkalosis
- Hyperuricaemia
- Allergic reactions

**11. Mannitol**

**Why is mannitol used in the management of head injury**

Used to reduce intracranial pressure

**What is the MOA?**

- Osmotic diuretic
- Alters starling forces as it does not cross the BBB so draws water out of the cells and reduces intracellular volume, hence reducing intracranial volume and intracranial pressure

**What are the other possible clinical effects?**

- Decreased intraocular pressure
- Diuresis, dehydration, hypovolaemia
- Hypernatraemia
- Hyperkalaemia

**What is the dose for raised ICP?**

0.25-2g per kg IV over 15 mins

**12. GTN and nitrites**

**By what routes can GTN be administered?**

Sublingual, transdermal, IV, oral, buccal, inhaled

**Why are parenteral routes favoured?**

To avoid the high first pass hepatic metabolism which significantly decreased the bioavailability

**What is the mechanism of action of GTN?**

- Taken up by vascular smooth muscle
- Interacts with sulfhydryl groups
- Releases nitric oxide
- Which activates cyclic GMP
- Dephosphorylates myosin light chains
- Reduces intracellular calcium levels
- Causes smooth muscle relaxation and vasodilation

**What are the clinical effects?**

- Causes venodilation, reduced venous return, decreased ventricular preload and therefore reduced myocardial oxygen consumption
- Higher doses can cause arterial dilation and decrease the systemic blood pressure
- Increased coronary collateral flow via vasodilation of epicardial arteries
- These effects improve myocardial oxygen delivery and relieve ischaemic pain
- Adverse effects include hypotension, tachycardia, headache, flushing, dry mouth

**What are the indications for GTN use in the ED?**

- Angina
- Acute coronary syndromes

- Hypertensive urgency/emergency
- APO
- Aortic dissection - used in combination with beta blockade

**What is meant by the term tachyphylaxis as it relates to GTN, and what is the implication of dosing?**
After continuous exposure to nitrates, smooth muscle may develop tolerance. This is due to reduced nitric oxide bioactivation secondary to depletion of tissue sulphydryl groups and decreased availability of cyclic GMP.
This is why we ensure a “drug free interval” of 8 hours between dosing.

**When should GTN be used with caution?**
Hypotension, sildenafil use, inferior and posterior myocardial infarction, fixed cardiac output stated (AS, tamponade), raised ICP, significant tachy/bradycardia and allergy.

**13. Hypertensive emergency**

**List some drugs used in hypertensive emergency**
GTN, nifedipine, hydralazine, sodium nitroprusside, labetolol, diazoxide, esmolol

**What are the pharmacokinetics of Na Nitroprusside**

- IV administration
- Onset in minutes - peak effect in minutes
- Half life 2 mins
- Duration of action 1- 10 mins
- Elimination in RBCs to cyanide, concerted in liver to thiocyanate which is renally cleared over 3 days

W**hat are the potential toxicities of Na nitroprusside?**

- Cyanide toxicity - hypotension, metabolic acidosis, pink skin, tachypnoea, decreased reflexes, dilated pupils
- Thiocyanate toxicity - ataxia, blurred vision, headache, nausea, vomiting, delirium