Drugs Used in the Management of Cardio-Vascular Disease.

Learning Objectives.

At the end of this course, you should be able to :

1. discuss the major groups of drugs used in the management of CV disease.
2. understand the mechanism of action of a range of drugs used in CV disease management.
3. make a link between basic pharmacokinetic and dynamic mechanisms and drug actions.
4. describe which groups of drugs are used in particular CV disorders.

1. The Heart.

Autonomic control of the heart

Both the parasympathetic and sympathetic nervous systems influence the heart. The sympathetic nervous system mediates its effects through the cardiac nerve, and activation of β_1-adrenoceptors. These are linked to adenylyl cyclase, and their activation causes increased levels of cyclic adenosine monophosphate (cAMP), and a subsequent increase in intracellular calcium levels. The effect this has on the heart is to increase the heart rate, increase the force of contraction, increase automaticity, encourage AV node conduction, and reduce the efficiency of the heart.

The parasympathetic nervous system mediates its effects through the vagus nerve, and activation of M_2- receptors. These are also linked to adenylyl cyclase, but their activation causes decreased levels of cAMP, and a subsequent decrease in intracellular calcium levels, the opposite to sympathetic action. The effect of this is to decrease the heart rate, decrease force of contraction, decrease automaticity, inhibit AV node conduction, and increase cardiac efficiency.

Cardiac contractility

Myocardial contraction is the result of calcium entry through L-type channels, giving rise to an increase in cytostolic calcium. The calcium comes from the sarcoplasmic reticulum within the cell, and also from the extracellular medium.

Extracellular calcium enters the cell, triggering larger amounts of calcium to be released from the sarcoplasmic reticulum (calcium-induced calcium release).

During contraction, the intracellular levels of calcium rise to levels 10 000 times greater than those at rest. Calcium binds to troponin C, affecting the position of actin and myosin filaments in the sarcomere, allowing the cell to contract.

Contraction ceases when calcium has been removed from the cytoplasm, when calcium is pumped out of the cell via the electrogenic Na+ /Ca^{z}+ exchanger, which pumps one calcium ion out for every three sodium ions in. Additionally, calcium is taken back into sarcoplasmic reticulum stores by a Ca^{z}+ ATPase pump.

Cardiac dysfunction

Congestive cardiac failure - Congestive cardiac failure (CCF) is the combined failure of both the left and right sides of the heart. The incidence of cardiac failure in the United Kingdom is between 1-5 per 1000 per year, and this doubles for each decade of life after the age of 45; over 100 000 hospital admissions annually are directly related to cardiac failure.

CCF occurs when the cardiac output does not meet the needs of the tissues. This is thought to result from defective excitation-contraction coupling, with progressive systolic and diastolic ventricular dysfunction. Signs of acute cardiac failure include rapid heart rate, hypotension, dyspnoea, and pulmonary and systemic oedema. In chronic cardiac failure there is extertional dyspnoea, systemic oedema, increase in heart size, fatigue, and orthopnoea. The body attempts to compensate for the effects of CCF by extrinsic and intrinsic processes.

Extrinsic neurohumoral reflexes: these aim to maintain cardiac output and blood pressure such that hypotension leads to the activation of baroreceptors (receptors responding to changes in pressure), in turn causing increased sympathetic activity, leading to increased heart rate and vasoconstriction, followed by increased cardiac contractility and vascular tone, and subsequently increased arterial pressure.

However, the greater the resistance (arterial pressure) against which the heart must pump reduces both the amount of oxygenated blood ejected by the heart, and the

perfusion of the tissues. The reduction in perfusion activates the renin-angiotensin system in the kidneys, leading to renin secretion and subsequent elevation of plasma angiotensin II and aldosterone levels. Angiotensin II causes peripheral vasoconstriction and aldosterone increases sodium retention, leading to increased water retention, oedema, and an increased preload.

Intrinsic cardiac compensation: increased cardiac preload leads to incomplete emptying of the ventricles and an increase in end-diastolic pressure.

The heart eventually fails, owing to the massive increase in energy requirements by the cardiac muscle.

Arrhythmias - Sudden death as a result of arrhythmias is the most common cause of death in developed countries, and it usually results from underlying cardiovascular pathology such as atherosclerosis. Myocardial ischaemia is one of the most important causes of arrhythmias, and it occurs when a coronary artery becomes occluded, preventing sufficient blood from reaching the myocardium. Accumulation of endogenous biological mediators, including potassium, cAMP, thromboxane A_2, and free radicals, are believed to initiate arrhythmias.

Reperfusion after coronary occlusion is necessary for tissue recovery and prevention of myocardial necrosis, but spontaneous resumption of coronary flow is often itself a cause of arrhythmias.

The two main mechanisms by which cardiac rhythm becomes dysfunctional are;

1. abnormal impulse generation (automatic or triggered)
2. abnormal impulse conduction.

In automatic abnormal impulse generation, sinus and atrial tachycardia are common, together with ventricular premature beats. It can be exacerbated by pathological conditions, such as ischaemia, which may affect nodal and conducting tissue so that their inherent pacemaker frequency is greater than that of the SAN. Ischaemia causes partial depolarization of tissues (owing to a decrease in the activity of the electrogenic sodium pump) and catecholamine release, enhancing the automaticity of the slow pacemakers (AVN, Purkinje fibres, bundle of His) and

often giving rise to an ectopic focus triggering the development of a premature beat. A premature beat may also develop in atrial or ventricular tissue, which is not normally automatic.

Abnormal impulse conduction includes heart block, which is likely to cause ventricular premature beats. It results from damage to nodal tissue (most commonly the AVN) caused by conditions such as infarction. AV block may be first, second, or third degree, manifesting itself from slowed conduction to complete block of conduction, where the atria and ventricles beat independently.

Angina pectoris - Angina is associated with acute myocardial ischaemia, and results from underlying cardiovascular pathology. When coronary flow does not meet the metabolic needs of the heart, a radiating chest pain results; this is angina pectoris.

Stable or classical angina is due to fixed stenosis of the coronary arteries, brought on by exercise and stress.

Unstable angina (crescendo angina) can occur suddenly at rest, and it becomes progressively worse, with an increase in the number and severity of attacks. The following conditions can all cause unstable angina:

- Coronary atherosclerosis.
- Coronary artery spasm.
- Transient platelet aggregation and coronary thrombosis.
- Endothelial injury causing the accumulation of vasoconstrictor substances.
- Coronary vasoconstriction following adrenergic stimulation.

Drugs used in heart failure and cardiac dysfunction .

a. Cardiac glycosides

Examples : digoxin, digitoxin.

Cardiac glycosides act by inhibiting the membrane Na+ /K+ ATPase pump, increasing the intracellular levels of sodium, thus reducing the sodium gradient across the membrane and decreasing the amount of calcium pumped out of the cell by the Na + /Ca^{2}+ exchanger during diastole. Consequently, the intracellular calcium concentration rises, leading to an increase in the force of cardiac contraction and maintaining normal blood pressure.

In addition, cardiac glycosides alter the electrical activity of the heart, both directly and indirectly. At therapeutic doses they indirectly decrease the heart rate, slow atrioventricular (AV) conductance and shorten the atrial action potential by stimulating vagal activity. This is useful in atrial fibrillation. At toxic doses they indirectly increase the sympathetic activity of the heart, and cause arrhythmias, including heart block. The direct effects are mainly due to loss of intracellular potassium, and they are most pronounced at high doses. The resting membrane potential is reduced, causing enhanced automaticity, slowed cardiac conduction, and increased A VN refractory period.

The increased cytostolic calcium concentration may reach toxic levels, thereby saturating the sarcoplasmic reticulum sequestration mechanism and causing oscillations in calcium owing to calcium-induced calcium release. This results in oscillatory after-potentials and subsequent arrhythmias.

In addition, cardiac glycosides have a direct effect on α-adrenoceptors, causing vasoconstriction and a consequent increase in peripheral vascular resistance, which is further enhanced by a centrally mediated increase in sympathetic tone.

These drugs have a very narrow therapeutic window, and toxicity is relatively common.

b. Phosphodiesterase inhibitors

Examples of phosphodiesterase (POE) inhibitors include enoximone and milrinone. These have been developed as a result of the many adverse effects and problems associated with cardiac glycosides. There is no evidence that these improve the mortality rate.

Phosphodiesterase is responsible for breaking down cAMP. By inhibiting it's action there is a rise in cAMP levels, causing an increase in myocardial contractility and vasodilatation. Cardiac output is increased, and pulmonary wedge pressure and total peripheral resistance are reduced, without much change in heart rate or blood pressure. Their adverse effects include nausea and vomiting, arrhythmias, liver dysfunction, abdominal pain, and hypersensitivity.

c. Beta-adrenoceptor agonists

Examples include propranolol, atenolol, bisoprolol, and metoprolol. Beta-adrenoceptors are found in many tissues, although there are sub-groups to be found in different tissues :

1. β_1-adrenoceptor - predominantly in the heart
2. β_2-adrenoceptor - mainly in the smooth muscle of the vasculature (although some overlap does exist).

Different β-blockers have a different affinity for the two types of adrenoceptor. Propranolol is non-selective, having equal affinity for both the β_1 and β_2 adrenoceptors. Atenolol, bisoprolol and metoprolol have greater affinity for the β_1 adrenoceptor, and are, therefore, more 'cardio-specific'. Some β-blockers even appear to have partial agonistic effects at β-adrenoceptors, as well as antagonistic effects.

The aim of using these drugs in cardiac disease is to block β-adrenoceptors in the heart. This has the effect of causing a fall in heart rate, reducing systolic blood pressure, reducing contractile activity, and therefore a reduction in oxygen demand from the heart.

Non-selective β-blockers (e.g. propranolol) must not be given to asthmatic patients. At high doses β_1-adrenoceptor antagonists lose their selectivity, and they should be used with caution in those with asthma. Other contraindications for β-blockers include bradycardia, hypotension, AV block, and CCF. Their side-effects include bronchospasm, fatigue and insomnia, dizziness, cold extremities due to activation of β_2-adrenoceptors, bradycardia, heart block, hypotension, and decreased glucose tolerance in diabetic patients.

d. Diuretics

The diuretics used in CCF are thiazides (bendrofluazide), loop diuretics (frusemide, bumetanide), and potassium-sparing diuretics (spironolactone, amiloride).

Diuretics inhibit sodium and water retention by the kidneys, and so reduce oedema due to heart failure. Venous pressure and consequently cardiac preload are reduced, increasing the efficiency of the heart as a pump.

Thiazide and related diuretics

Bendroflumethiazide (bendrofluazide), chlortalidone, metolazone, and indapamide are examples of thiazide diuretics. Thiazides produce a moderately potent diuresis, causing the excretion of 5-10% of filtered sodium. Their site of action is on the distal convoluted tubule. They work by inhibiting the Na^+/Cl^- co-transporter in the luminal membrane. They increase the secretion of potassium and protons into the collecting ducts but they also decrease calcium excretion by a mechanism possibly involving the stimulation of a sodium/calcium exchange across the basolateral membrane; this is due to reduced tubular cell sodium concentration. Their adverse effects include hypokalaemia, hyponatraemia, or hypercalcaemia. Caution is needed when prescribing to those taking cardiac glycosides, or patients with diabetes mellitus as thiazides may cause hyperglycaemia.

Loop diuretics

Frusemide (furosemide), bumetanide, and torasemide are examples of loop diuretics. Loop diuretics cause the excretion of 15-25% of filtered sodium as opposed to the normal 1 % or less. This can result in a profound diuresis. Loop

diuretics act at the thick ascending segment of the loop of Henle. Their action is to inhibit the $Na^+/K^+/2Cl^-$ co-transporter in the luminal membrane. This increases the amount of sodium reaching the collecting duct and, thereby, increases potassium and proton secretion. Calcium and magnesium reabsorption is also inhibited, owing to the decrease in potential difference across the cell normally generated from the recycling of potassium. Loop diuretics additionally have a venodilator action, which often brings about relief of clinical symptoms prior to the onset of diuresis.

Loop diuretics should not be given to those with severe renal impairment. They should be given only with extreme caution to patients receiving:

- cardiac glycosides, as the hypokalaemia caused by loop diuretics potentiates the action of cardiac glycosides and consequently increases the risk of cardiac glycoside-induced arrhythmias .
- aminoglycoside antibiotics, as these interact with loop diuretics and increase the risk of ototoxicity and potential hearing loss.

Possible adverse effects include hypokalaemia, hyponatraemia, hyperuricaemia, hypotension, and hypovolaemia. Metabolic alkalosis may occur because of increased proton secretion, and consequent excretion. Hypocalcaemia and hypomagnesaemia are also possible.

Potassium-sparing diuretics

Spironolactone, amiloride, and triamterene are all potassium-sparing diuretics. Potassium-sparing diuretics produce mild diuresis, and they cause the excretion of 2-3% of filtered sodium. They work at the late distal tubule and collecting duct.

There are two classes of potassium-sparing diuretics:

- Sodium-channel blockers, e.g. amiloride and triamterene. These drugs block sodium reabsorption by the principal cells, thus reducing the potential difference across the cell and reducing potassium secretion. Secretion of proton from the intercalated cells is also decreased .

- Aldosterone antagonists, e.g. spironolactone. This is a competitive antagonist at aldosterone receptors, and thus reduces sodium reabsorption and, therefore, potassium and proton secretion. The degree of diuresis depends on aldosterone levels.

Potassium-sparing diuretics interact with angiotensin-converting enzyme inhibitors, increasing the risk of hyperkalaemia. They should not be given to patients with renal failure. Adverse effects include gastrointestinal disturbances, hyperkalaemia, and hyponatraemia. Aldosterone antagonists have a wide range of adverse effects, including gynaecomastia, menstrual disorders, and male sexual dysfunction.

Interestingly, lower doses of spironolactone have beneficial effects in CCF. Several preparations exist which combine a potassium-sparing diuretic with either a thiazide or a loop diuretic, e.g. co-amilofruse, which contains amiloride and frusemide.

e. Angiotensin-converting-enzyme inhibitors

Examples of these drugs include captopril, enalopril, lisinopril, and ramipril. They case inhibition of angiotensin converting enzyme (ACE), leading to a reduction of levels of angiotensin II and aldosterone levels, as well as increased bradykinin levels. This leads to vasodilation and a reduction in peripheral resistance. However, this does not change the cardiac output or heart rate. Adverse effects include a characteristic dry cough, hypotension, dizziness, headaches, diarrhoea, and muscle cramps. After a first dose, there is often a profound drop in blood pressure, so it is best that the drug is taken at night, before going to bed.

f. Nitrates

Glyceryl trinitrate and isosorbide mononitrate are organic nitrates used in the immediate relief of angina. Most nitrates are pro-drugs which quickly decompose to produce nitric oxide, which in turn activates guanyl cyclase. This increases the levels of cyclic GMP, activating protein kinase G, and phosphorylating contractile proteins. The subsequent dilation of the systemic veins decreases the preload, and thereby reduces oxygen requirements of the cardiac tissue, whilst dilation of the

coronary arteries leads to an increase in blood flow and oxygen delivery to the cardiac muscle.

These drugs are usually administered sublingually, orally in a modified release form, of via transcutaneous patch. They are not given to patients with hypotension. Side effects include postural hypotension, tachycardia, headache, flushing, and dizziness. To avoid the possibility of nitrate tolerance, a drug-free period of around 8 hours is required.

g. Anti-arrhythmic drugs

Antiarrhythmic drugs are classified according to a system devised by Vaughan Williams in 1970 (later modified by Harrison), in which there are six classes of drug.

Class I

All Class I drugs block the voltage-dependent sodium channels in a dose-dependent manner in a similar way to local anaesthetics. They prolong the effective refractory period, and they convert unidirectional block to bidirectional block (prevent re-entry).

Class Ia – e.g.quinidine, procainamide. Class la drugs affect atrial muscle, ventricular muscle, the bundle of His, the Purkinje fibres, and the AVN. By blocking the voltage-dependent sodium channels in their open or closed state they prevent re-entry of ions, thereby prolonging the refractory period. They are indicated for ventricular and supraventricular arrhythmias. Side effects include arrhythmias, nausea and vomiting, hypersensitivity, thrombocytopenia, and agranulocytosis.

Class Ib – e.g lignocaine, phenytoin. These drugs exert their effects in several ways. These include:

- Blocking voltage-dependent sodium channels in , their refractory (inactivated) state, i.e. when depolarized, as occurs in ischaemia.
- Binding to open channels, and dissociating by the next beat if the rhythm is

normal, but abolishing premature beats.

- Decreasing action potential duration.
- Increasing the effective refractory period.

Lignocaine is administered intravenously, and phenytoin either orally or intravenously. They are usually given for ventricular arrhythmias following myocardial infarction. Phenytoin is also used in epilepsy management. Class Ib drugs should not be given to patients with sinoatrial disorders, AV block, and porphyria. Lignocaine may cause dizziness and respiratory depression, whilst phenytoin may cause nausea and vomiting, and peripheral neuropathy.

Class Ic - Flecainide is the only drug used from class Ic. It blocks sodium channels in a fashion similar to the class Ia and Ib drugs, but it shows no preference for refractory channels. Class Ic drugs result in a general reduction in the excitability of the myocardium. They are sued for ventricular tachyarrhythmias.

Class II

Examples of class II drugs include propranolol, atenolol, metoproplol, and pindolol

Class II drugs are β -adrenoceptor antagonists (atenolol is β_1- selective). They have been shown to reduce sudden death after myocardial infarction by 50%, although this may be due to prevention of cardiac rupture as opposed to prevention of ventricular fibrillation.

Class III

Examples of Class III drugs include bretylium, amiodarone, sotalol, and ibutilide.

These drugs act as potassium channel blockers. They prolong cardiac action potential duration, and they prolong the effective refractory period. Amiodarone also blocks sodium and calcium channels.

Class III drugs are given for ventricular and supraventricular arrhythmias.

Class IV

Examples of class IV drugs include verapamil and diltiazem.

Class IV drugs are calcium antagonists that shorten the length of the action potential, thus decreasing action potential duration.

h. Calcium-channel blockers

Examples of calcium-channel blockers include verapamil, diltiazem, and nifedipine. They produce their effect by blocking L-type calcium channels found in the heart and vascular smooth muscle, thereby reducing calcium entry into cardiac and vascular cells. This decrease in cytostolic calcium reduces cardiac contractility and causes vasodilatation, which reduces preload due to the reduced venous pressure; it also reduces afterload due to the reduced arteriolar pressure; it increases coronary blood flow; reduces cardiac contractility thereby reducing myocardial oxygen consumption; decreases heart rate. High doses of these drugs affect AV nodal conduction.

Nifedipine blocks L-type calcium-channels in vascular cells. It does not affect cardiac contractility, nor AVN conduction, and its beneficial effects are due to increased coronary flow and peripheral vasodilatation.

Calcium-channel blockers are used for the prevention and treatment of angina and hypertension. Verapamil and diltiazem are given for supraventricular arrhythmias, and nifedipine for Raynaud's syndrome (peripheral vasoconstriction).

Verapamil and diltiazem may cause hypotension, rash, bradycardia, CCF, heart block, and constipation. Nifedipine may cause hypotension, rash, tachycardia, peripheral oedema, flushing, and dizziness.

i. Antianginal drugs

Acute attacks of angina are treated with sublingual nitrates. Stable angina is treated with long-acting nitrates, anti platelets, β -adrenoceptor antagonists, calcium antagonists, or potassium-channel activators. Unstable angina is a medical

emergency, and it requires hospital admission. Unstable angina is treated with:

- Antiplatelets (aspirin, clopidogrel, dipyridamole and the glycoprotein IIb/IIIa inhibitors).
- Heparin/low-molecular weight heparin.
- Standard anti anginal drug regimen.

Organic nitrates – discussed previously.

Calcium-channel blockers – discussed previously.

Potassium-channel activators

Nicorandil is the only licensed drug in this class. It acts to activate the potassium channels of the vascular smooth muscle. Once activated, potassium flows out of the cells, causing hyperpolarization of the cell membrane. The hyperpolarized membrane inhibits the influx of calcium, and, therefore, inhibits contraction-the overall effect is relaxation of the smooth muscle, and vasodilatation. They are given for the prevention of angina, and side-effects include headache, cutaneous vasodilatation, nausea, and vomiting.

KEY LEARNING POINTS.

1. **CCF occurs when the cardiac output does not meet the demands of the tissues.**
2. **Arrhythmia is the commonest cause of sudden death in developed countries.**
3. **Beta-blockers are used to bring about a fall in the heart rate, reducing systolic pressure and oxygen demand.**
4. **Cardio-selective beta-blockers are used to avoid action at non-cardiac beta-receptors.**
5. **Diuretics inhibit sodium and water retention in the kidney, reducing volume, and increasing the efficiency of the heart.**
6. **Thiazide diuretics can cause hyperglycaemia.**
7. **Loop diuretics are very effective, but may cause hypokalaemia.**
8. **ACE inhibitors reduce the levels of angiotensin II, leading to a reduction in vasoconstriction.**
9. **Calcium channel blockers prevent the influx of calcium ions into cardiac muscle, reducing its ability to contract, decreasing heart rate and oxygen demand.**

2. The Circulation.

Control of vascular tone

Alpha-adrenoceptors - activation causes contraction of vascular smooth muscle through the activation of phospholipase C. The resulting increased level of IP_3 causes the release of calcium from the endoplasmic reticulum, increasing calcium levels. Calcium then binds to calmodulin, activating myosin light-chain kinase (MLCK) and allowing contraction.

$Beta_2$-adrenoceptors - activation causes relaxation of vascular smooth muscle through the activation of adenylyl cyclase. The resulting increased level of cAMP activates protein kinase A, which phosphorylates and inactivates MLCK.

M_3 receptors - activation causes relaxation of vascular smooth muscle through the release of endothelium-derived relaxing factor (EDRF), which is believed to be nitric oxide. Guanylyl cyclase is activated by NO, thus increasing the levels of cGMP and activating protein kinase G. Protein kinase G inhibits contraction by phosphorylating contractile proteins.

Renin-angiotensin system - decrease in plasma volume results in the activation of the renin-angiotensin system (RAS). Angiotensin-converting enzyme (ACE) catalyses the production of angiotensin II, leading to :

- Potent vasoconstriction (40 times as potent as noradrenaline).
- Release of noradrenaline.
- Stimulation of the secretion of aldosterone.

ACE also catalyses the inactivation of bradykinin, which is an endogenous vasodilator.

Aldosterone is a steroid that induces the synthesis of sodium channels and Na + /K+ ATPase pumps in the luminal membrane of the cortical collecting ducts. This results in a greater amount of sodium and water being reabsorbed, thus increasing the blood volume and pressure. Certain renal diseases and renal artery occlusion will cause activation of the RAS and result in the development of hypertension.

Hypertension

Normal blood pressure is generally regarded as 120/80 mmHg (systolic pressure/ diastolic pressure) Hypertension is defined as a diastolic arterial pressure greater than 90 mmHg, or a systolic arterial pressure greater than 140 mmHg. The condition can be fatal if left untreated, as it greatly increases the risk of thrombosis, stroke, and renal failure. Three factors determine blood pressure - blood volume, cardiac output, and peripheral vascular resistance.

'Primary' or 'essential' hypertension accounts for 90-95% of all cases of hypertension. This has no known cause, but it is associated with factors such as age (40+), obesity, physical inactivity, smoking and alcohol consumption, and a genetic predisposition.

'Secondary hypertension' accounts for the remaining 5-10% of cases of hypertension. The cause is usually related to systemic disease such as renal or endocrine disease.

Drugs used in the management of hypertension

a. Vasodilators

Angiotensin-converting enzyme inhibitors – previously discussed.

Angiotensin-II receptor antagonists

Losartan and valsartan are examples of angiotensin-Il receptor antagonists. They cause inhibition at the angiotensin II receptor, resulting in vasodilatation with a consequent reduction in peripheral resistance. They are given orally, and side effects include a cough (less common than with ACE inhibitors), orthostatic hypotension, dizziness, headache and fatigue, hyperkalaemia, and rashes.

Calcium antagonists – previously discussed.

Alpha$_1$-adrenoceptor antagonists.

e.g. Prazosin, doxazosin. These drugs cause inhibition of α_1- adrenoceptor-mediated vasoconstriction, thereby reducing peripheral resistance and venous pressure. They also lower plasma low-density lipoprotein (LDL) cholesterol levels, very-low-density lipoprotein (VLDL) levels, and triglyceride (TGA) levels, and increase high-density lipoprotein (HDL) cholesterol levels, reducing the risk of coronary artery disease. Their use can result in postural hypotension, dizziness, headache and fatigue, weakness, palpitations, and nausea.

Hydralazine

Hydralazine is a second- or third-line drug for the treatment of mild to moderate hypertension. Its effects are unclear, though it appears to interfere with the action of IP_3 in vascular smooth muscle, thereby reducing peripheral resistance and blood pressure. They are used in moderate to severe hypertension, and in conjunction with β -blockers and thiazides in hypertensive emergencies, and in hypertensive pregnant women.

Minoxidil

This drug has major adverse effects and so is used as a last resort in hypertension management. It activates of vascular smooth muscle ATP-sensitive potassium channels, resulting in hyperpolarization of the cell membrane and consequent reduced calcium entry through L-type channels. The overall effect is inhibition of smooth muscle contraction, and subsequent vasodilatation. It can cause hair growth, but also sodium and water retention, tachycardia, and cardiotoxicity.

b. Diuretics.

Although discussed previously these drugs are worth discussing further. The antihypertensive action of diuretics does not seem to fit well with their diuretic activity. Loop diuretics only produce a moderate antihypertensive action but are powerful diuretics, where as thiazides are moderate diuretics, but powerful antihypertensives. Antihypertensive effects of diuretics may not be a result of their diuretic affect but perhaps due to their activation of the ATP-regulated potassium channels in the arterioles, which control peripheral resistance.

KEY LEARNING POINTS.

1. **Vascular tone is controlled via the activity of alpha-adrenoceptors, beta-adrenoceptors, and muscarinic receptors.**
2. **The renin-angiotensin system is also involved in control of vasomotor tone.**
3. **Primary hypertension is associated with factors such as age, smoking, obesity.**
4. **Secondary hypertension is related to the presence of systemic disease, such as renal disease, or diabetes.**
5. **Vasodilating drugs are used to increase the lumen of blood vessels, thereby reducing the pressure exerted on the blood.**
6. **Drugs which interfere with the production of angiotensin II will help promote vasodilation.**

3. Lipoprotein Circulation & Atherosclerosis.

Lipids are insoluble, and are transported in the blood via lipoproteins. There are four types of these :

- High-density lipoproteins (HDL)
- Low-density lipoproteins (LDL)
- Very-low-density lipoproteins (VLDL)
- Chylomicrons

Additionally, lipid transport is via endogenous or exogenous pathways;

Exogenous	Endogenous
Diet-derived lipid breakdown leads to the formation of chylomicrons.	The liver secretes VLDLs, the components of which may be derived either endogenously or from the diet.
Lipoprotein lipase (LPL), found in the endothelium of extrahepatic tissues, hydrolyses the triglycerides in chylomicrons to glycerol and free fatty acids (FFAs), for use by the tissues.	Lipoprotein lipase (LPL), found in the endothelium of extrahepatic tissues, hydrolyses triglycerides in the VLDLs to glycerol and FFAs, for use by the tissues, and leaves LDL.
The chylomicron remnant is taken up by the liver.	LDL is then taken up by the liver and extrahepatic tissues.
The liver secretes cholesterol and bile acids into the gut, creating an enterohepatic circulation.	HDL is secreted by the liver into the plasma, where it is modified by lecithin cholesterol acyltransferase (LCAT) and uptake of cholesterol from the tissues. Lecithin cholesterol acyltransferase (LCAT) transfers cholesterol esters to LDLs and VLDLs.

Hyperlipidaemias

Hyperlipidaemias are characterised by markedly elevated plasma triglycerides, cholesterol, and lipoprotein concentrations. Cholesterol is deposited in various tissues. Deposition in arterial plaques results in atherosclerosis, which leads to heart attacks, strokes, and peripheral vascular disease. Deposition in tendons and skin results in xanthomas.

Primary - Primary hyperlipidaemias are genetic, and numerous types exist.

Secondary - Secondary hyperlipidaemias are the consequences of other conditions such as:

- Diabetes
- Liver disease
- Nephrotic syndrome
- Renal failure
- Alcoholism
- Hypothyroidism
- Oestrogen administration.

Treatment with lipid-lowering drugs.

a. HMG CoA reductase inhibitors ('statins')

Atorvastatin, pravastatin, and simvastatin are examples of 3-hydroxy-3-methylglutaryl coenzyme A (HMG CoA) reductase inhibitors. These drugs have been shown to reduce blood cholesterol by up to 35% in some patients. HMG CoA reductase inhibitors can reduce the risk of dying from a coronary event by up to nearly half. They work by reversibly inhibiting the enzyme HMG CoA reductase, which catalyses the rate-limiting step in the synthesis of cholesterol. The decrease in cholesterol synthesis also increases the number of LDL receptors, thus decreasing LDL levels. Side effects include reversible myositis (rare),constipation or diarrhoea, abdominal pain and flatulence, nausea and headache, fatigue and insomnia, and rashes.

b. Fibrates

Fibrates include bezafibrate, ciprofibrate and gemfibrozil. These are broad-spectrum lipid-modulating agents that are ineffective in patients with elevated cholesterol but normal triglyceride concentrations. They work in a number of ways:

1. stimulation of lipoprotein lipase, thus reducing the triglyceride content of VLDLs and chylomicrons;
2. stimulation of hepatic LDL clearance, by increasing hepatic LDL uptake;
3. reduction of plasma triglyceride, LD L and VLDL concentrations;
4. increase of HDL-cholesterol concentration (except bezafibrate).

Gemfibrozil also decreases lipolysis and may decrease VLDL secretion.

Side effects of fibrates include myositis-like syndrome (especially if renal function is impaired), GI disturbances, dermatitis, pruritus, rashes,urticaria, impotence, headache, dizziness, blurred vision.

KEY LEARNING POINTS.

1. **There are four types of lipoprotein – HDL, LDL, VLDL, and chylomicrons.**
2. **Their role is to transport lipids in the blood.**
3. **Increased levels of these lipoproteins can result in atherosclerotic plaque development.**
4. **Statins can reduce blood cholesterol levels by up to 35%. They work by decreasing the production of cholesterol, and increasing numbers of lipoprotein receptors.**
5. **Fibrates work by reducing the levels of lipoproteins.**

4. Haemostasis and thrombosis

Principles of haemostasis

If haemostasis is defective or unable to cope with blood loss from larger vessels, blood may accumulate in the tissues. This accumulated blood is called a haematoma.
The three stages involved in haemostasis are

- blood vessel constriction,
- formation of a platelet plug,
- formation of a clot.

Blood vessel constriction - The first response to a severed blood vessel is contraction of the smooth muscle of the vessel. This is mediated by the release of thromboxane A2 and other substances from platelets. Blood vessel constriction slows the flow of blood through the vessel, thus reducing the pressure, and pushes opposing surfaces of the vessel together. In very small vessels this results in permanent closure of the vessel, but in most cases blood vessel constriction is insufficient for this to occur.

Platelet plug formation - Exposure to the collagen underlying the vessel endothelium allows platelets to adhere to the collagen by binding to von Willebrand's factors. These factors, secreted by the platelets and endothelium, bind to the exposed collagen; platelets then bind to this complex. Release of ADP, 5-HT, thromboxane A2, and other substances by the platelets causes the latter to aggregate, while fibrin acts to bind them together. The synthesis and release of prostacyclin by the intact endothelium inhibits platelet aggregation, this acts to limit the extent of the platelet plug. Intact endothelial cells also produce nitrous oxide, a vasodilator and inhibitor of platelet aggregation

Clot formation - Blood coagulation is the conversion of liquid blood into a solid gel, known as a clot. A clot consists of a meshwork of fibrin within which blood

cells are trapped. It functions to reinforce the platelet plug. Fibrin is formed from its precursor fibrinogen through the action of an enzyme called thrombin

The formation of thrombin occurs both intrinsically and extrinsically, and together these are known as the coagulation cascade. Both pathways involve the conversion of inactive factors into active enzymes, which then go on to catalyse the conversion of other factors into enzymes.

The extrinsic pathway is so called because the component needed for its initiation is contained outside the blood. Tissue factor binds factor VII on exposure of blood to subendothelial cells, and converts it to its active form, VIIa. This enzyme catalyses the activation of factors X and IX.

The intrinsic pathway is so called because its components are contained within the blood. It combines with the extrinsic pathway at the step prior to thrombin activation. The thrombin formed stimulates the activation of factors XI, VIII, and V, and thus acts as a form of positive feedback.

Three naturally occurring anticoagulants limit extent of clot formation. These are:

- Tissue factor pathway inhibitor - binds to the tissue factor-VIIa complex, and inhibits its actions.
- Protein Q - activated by thrombin, and inactivates factors VII and V
- Antithrombin III - which is activated by heparin and inactivates thrombin and other factors.

Fibrinolysis – the fibrinolytic or thrombolytic system functions to dissolve a clot once repair of the vessel has begun. Plasmin is formed from plasminogen through the action of plasminogen activators, and its role is to break down fibrin.

Thrombosis - thrombosis is the pathological formation of a clot, known as a thrombus, which may cause occlusion within blood vessels or the heart, and result in death. Thrombosis can lead to arterial occlusion, which may lead to myocardial

infarction, stroke, and peripheral ischaemia. It can also lead to venous occlusion, which may lead to deep venous thrombosis and pulmonary embolism.

Arterial thrombi form because of endothelial injury, itself the result of underlying arterial wall pathologies such as atherosclerosis. Venous and atrial thrombi tend to form as a result of blood stasis, allowing the build-up of platelets and fibrin.

Treatment of heamostatic disorders.

Hereditary bleeding disorders are relatively rare. Haemophilia is a genetic disorder in which excessive bleeding occurs, owing to the absence of factor VIII (haemophilia A) or IX (haemophilia B). Von Willebrand's disease is characterized by abnormal bruising and mucosal bleeding. Acquired bleeding disorders may be due to liver disease, vitamin K deficiency, or anticoagulant therapy.

a. Vitamin K.

Vitamin K is needed for the post-transcriptional, carboxylation of glutamic acid residues of prothrombin (factor II) and clotting factors VII, IX, and X by the liver It is also necessary for normal calcification of bone.

It is administered either orally, intramuscularly, or intravenously. It is used as an antidote to the effects of oral anticoagulants (such as warfarin), and in patients with biliary obstruction or liver disease, where Vitamin K deficiency may be a problem. It is also used after prolonged treatment with antibiotics that inhibit the formation of vitamin K by intestinal bacteria, and as prophylaxis against hypoprothrombinaemia in the newborn.

Side effects of vitamin K include haemolytic anaemia and hyperbilirubinaemia in the newborn.

b. Protamine.

Protamine is a strongly basic protein, which forms an inactive complex with heparin, and as such is used in patients in whom heparin treatment has resulted in

haemorrhage. High doses of protamine appear to have anticoagulant effects through an unknown mechanism.

c. Clotting factors

Deficient clotting factors can be replaced by the administration of fresh plasma. Factors VIII and IX are available as freeze-dried concentrates.

d. Desmopressin

Desmopressin is a synthetic analogue of vasopressin. It causes the release of factor VII. Desmopressin is also used in diabetes insipidus as it has anti-diuretic effects. Desmopressin is given for mild factor VIII deficiency, but its side effects include fluid retention, hyponatraemia, headache, nausea, and vomiting.

e. Anticoagulants

Vitamin K antagonists

Warfarin, acenocoumarol (nicoumalone), and phenindione are examples of vitamin K antagonists. These drugs block the reduction of vitamin K epoxide, which is necessary for its action as a cofactor in the synthesis of factors II, VII, IX, and X They are given orally for the prophylaxis and treatment of deep vein thrombosis and pulmonary embolism; the prophylaxis of embolisation in atrial fibrillation and rheumatic disease, and in patients with prosthetic heart valves. The onset of action of vitamin K antagonists takes several hours, owing to the time needed for the degradation of factors that have already been carboxylated.

Heparin and the low-molecular weight heparins

Heparin activates antithrombin III, which limits blood clotting by inactivating thrombin and factor X. Heparin also inhibits platelet aggregation, possibly as a result of inhibiting thrombin. Low-molecular weight heparins are simply fragments of heparin which exhibit very similar activity to heparin.

They are usually given intravenously or subcutaneously. Heparin is given by intravenous infusion, or 12 hourly by the subcutaneous route. Low-molecular

weight heparins are given as a once daily subcutaneous injection. Heparin has an immediate onset, and it can, therefore, be used in emergencies.

Hirudins

These are derived from medical leeches, and work by inactivating thrombin, e.g. desirudin, lepirudin. Desirudin is used in patients with heparin-induced thrombocytopenia, and for the prophylaxis of deep-vein thrombosis in patients undergoing hip and knee replacement.

f. Antiplatelet agents

Aspirin

Aspirin is acetylsalicylic acid, and originally derived from the bark of willow tree. Aspirin blocks the production of thromboxane A2 from arachidonic acid in platelets by inhibiting the action of the enzyme cyclooxygenase. Thromboxane A2 stimulates phospholipase C, thus increasing calcium levels and causing platelet aggregation. Aspirin also blocks the synthesis of prostacyclin from endothelial cells, inhibiting platelet aggregation. However, this effect is short lived because endothelial cells can synthesize new cyclooxygenase.

Aspirin in used in the prevention and treatment of myocardial infarction and ischaemic stroke. It is also used as an analgesic and an anti-inflammatory agent. Aspirin at 150 mg daily after myocardial infarction has been shown to decrease mortality significantly. Given on alternate days, it may reduce the incidence of primary myocardial infarction.

Dipyridamole

Dipyridamole causes inhibition phosphodiesterase, which hydrolyses cAMP. The resulting increased cAMP levels result in decreased calcium levels and inhibition of platelet aggregation. It is usually used in conjunction warfarin and other oral anticoagulants in the prophylaxis of thrombosis associated with prosthetic heart valves.

Clopidogrel

Clopidogrel inhibits activation the glycoprotein IIb/IIIa receptor on the surface of platelets, which is required for platelet aggregation. It is used in the secondary prevention of cardiovascular and cerebrovascular events. For those patients who cannot tolerate aspirin, clopidogrel can be used in its place.

g. Fibrinolytic agents

Streptokinase

Streptokinase forms a complex with and activates plasminogen into plasmin, a fibrinolytic enzyme. It is used for acute venous thrombosis, pulmonary embolism, arterial thromboembolism, and acute myocardial infarction. Streptokinase is commonly used in conjunction with antiplatelet and anticoagulant drugs.

Streptokinase is derived from haemolytic streptococci, and it is therefore antigenic. Repeated administration of streptokinase could result in an anaphylaxis -like reaction. If repeated fibrinolytic therapy is needed, the non-antigenic tissue-type plasminogen activators should be employed.

Tissue-type plasminogen activators (t-PAs)

Alteplase and reteplase are examples of t-PAs, and work as plasminogen activators. They are used in the management of myocardial infarction and pulmonary embolism.

KEY LEARNING POINTS.

1. **Heamostasis involves blood vessel constriction, platelet plug formation, and clot development.**
2. **Fibrinolysis occurs to remove a blood clot once repair is complete.**
3. **Disorders of clotting can cause the development of thrombi.**
4. **Vitamin K is essential in the blood clotting cascade. It can be given as an antidote to overdose of warfarin.**
5. **Warfarin works by antagonising Vitamin K, increasing the time it takes for a clot to form. It is given orally for the prevention of deep vein thrombosis and pulmonary embolism.**
6. **Heparin inactivates thrombin and Factor X, preventing blood clotting.**
7. **Antiplatelet drugs prevent the aggregation of platelets, which is usually the first step in the formation of a clot.**
8. **Aspirin inhibits the activity of cyclooxygenase, preventing the production of thromboxane A2, prostaglandins, and prostacyclins.**
9. **Dipyridamole inhibits phosphodiesterase activity, resulting in decreased calcium levels, inhibiting platelet aggregation.**
10. **Clopidogrel is an alternative anti-platelet if aspirin cannot be used.**