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DRUGS AFFECTING THE HEART AND CARDIOVASCULAR SYSTEM

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Antihypertensive Drugs

Hypertension is a vascular disease with an elevated level of bp recorded over a period of time.

There are three types of hypertensions:

1. primary / essential : age related changes in the nervous, cv and endocrine systems. Two common symptoms that are noted are nocturia and headache.
2. Secondary : is due some other consequence such as pregnancy, arteriosclerosis or renal disease.
3. Malignant: in this case hypertension develops quickly and can be severe enough to cause a cerebral oedema. These can be caused due to some agents such as MOAI or eclampsia.

Chronic hypertension leads to the thickening of the walls of the artery and arterioles and also leads to the narrowing of the lumen. Other layers of the wall undergo fibrosis. This damage induces an inflammatory response that increases the permeability of the vascular endothelium.

The aim of the antihypertensive drugs is to lower the bp and prevent damage to major body organs and other tissues. This is rarely achieved by monotherapy and hence a combined therapy is common and can lead to an increase in the

complexity of the drug regimen and incidence of adverse effect and can lead to non – compliance of the drug treatment.

Two factors determine the bp that is cardiac output (stroke vol x heart rate) and systemic vascular resistance (SVR) of the vasculature. It is regulated by the interaction of the nervous, humoral and renal system.

The bp is measured by the sensory receptors located in the walls of the artery which are sensitive to change in pr and chemistry of the blood. These receptors are found in the aortic arch and in the common carotid arteries. These receptors relay their information to the vasomotor centers in the medulla via the afferent fibers associated with the glossopharangeal cranial nerve. The vasomotor center is part of the sns and its function is regulated with the help of alfa2 – adrenergic receptors. The efferent fibers descend the spinal cord and enter the periphery between the T1 and L2 levels. These fibers stimulate the smooth muscle causing vasoconstriction and as a result inc SVR and cardiac output as a result there is inc bp. The medulla also contains fibers that stimulate the force of contraction of the heart and heart rate thereby leading to an inc in bp.

Humoral control system:

Endocrine – renal interactions

These comprise of hormones and other vasoactive substance which are either secreted from the glands or from the walls of the blood vessels and either cause dilation or constriction of the blood vessels.

Most imp humoral mechanism is the rennin – angiotensin system, which regulates renal blood flow. When there is a dec in bp of the renal blood flow rennin an enzyme is released from the renal arterioles. This converts the plasma protein angiotensinogen into angiotensin I, which then converted into an active vasoconstrictive product angiotensin II with the help of angiotensin converting enzyme, this inc the blood flow thru the kidney and as a result there is an inc in bp.

Vasopressin known as an antidiuretic also has an effect of inc the bp by inc the absorption of water.

Adrenaline and noradrenalin also inc bp by vasoconstriction.

Endothelial vasoactive substances: are endothelins, pg's, and nitric oxide.

Endothelin acts as a locally acting vasoconstrictor. Pg's and nitric oxide are potent vasodilators

Antihypertensive therapies:

There is the ABCDE therapy: as follows:

A : ACE inhibitors

B: beta blockers

C: Ca Channel blockers

D: Diuretics

E: Endothelin receptor antagonist.

ACE Inhibitors: these drug group act on the rennin – angiotensin system by preventing the conversion of angiotensin I to angiotensin II as a result of which there is a dec SVR and hence lowered bp. Angiotensin also stimulates the aldosterone, sodium and water retention are also diminished. It also prevents the breakdown of a vasodilator peptide called bradykinin which makes a further contribution to the dec in vascular resistance. The reduction of bp is brought about without lowering the cardiac output. It is the choice of drug for congestive heart failure since it reduces the work load of the heart without reducing the cardiac output. Captopril is the prototype and is prodrug which is converted into its active form once absorbed and this is so since the drug on its own is poorly absorbed. Common side effects are hypotension, dizziness and headache. Induce cough and hyperkalaemia.

Angiotensin receptor antagonist:

Losartan, irbesartan, candesartan... they are similar in action to the ACE I and cause a dec in SVR and an dec in the release of aldosterone. They do not inhibit the formation of angiotensin II, they rather produce the effect by blocking the interaction of angiotensin II with the specific receptor. The common side effects are dizziness, headache, hypotension and GI disturbances.

Alfa 1 antagonist: are designed to block the alfa 1 receptor located on the arteriole and venule. These receptors mediate vasoconstriction hence blocking them lowers the SVR. Common side effects are postural hypotension, nasal congestion, pupil constriction, fatigue, inhibition of ejaculation and diarrhea.

For all the three types the diuretics are withheld when the course of the drug is being started.

Beta – blockers: though have been used for a long time their mechanism is unclear. It takes about a week or two to manifest . it is suggested that the rennin release is mediated by the beta 1 receptors and hence blocking of these receptors results in a dec in pdtn of angiotensin II and also aldosterone resulting in a dec in the SVR and also bp. Common adverse effects include bradycardia, hypotension, cold extremities, vivid dreams and constipation. Blocking of the beta 2 receptors leads to bronchoconstriction and hence can cause an asthma attack.

Calcium Channel Blockers: management of angina pectoris and cerebral ischaemia, selected cardiac dysrhythmias and hypertension.

Ca channels regulate the influx of ca across the membrane of the muscle cells. They play a particular role in the heart and vascular smooth muscle. Ca channel antagonist dec the influx of ca across the membrane and as a result dec the amt of ca even in the heart and blood vessels and ca ions are required for the contraction of the muscles. Cardiac contractility, conduction and tone is affected. These are divided into three subtypes:

Nifedipine like agents: nifedipine, felodipine, amlodipine: also known as dihydropyridine. These are relatively selective for vascular muscle

Diltiazem : depresses heart and vascular muscle and

Verapamil : depresses cardiac and vascular muscle as well as atrioventricular node.

Common side effects are hypotension, headache, facial flushing and skin rash, can lead to bradycardia and other cardiac dysrhythmias. These are not recommended for long term management of people with heart failure.

Drugs with a combined action: labetalol and Celiprolol are sympathetic depressants that peripherally block all the adrenoceptors. The adv is that there is resultant dec in bp at the alfa and beta sites but the disadv that the adverse effects of both will occur. Common side effects are hypotension, dizziness and bradycardia.

Diuretics : lower bp by reducing the vol of blood and this is achieved by inc the amount of water excreted as urine. The problem associated with this is dehydration, hypotension and electrolyte imbalance. Thiazide diuretics, potassium – sparing diuretics and diuretic drug with a mixed action (indapamide), loop diuretics (frusemide)

Hypertensive emergencies and second line hypertensive therapies:

Peripheral vasodilators are used in the treatment of second line hypertensive therapy. These reduce the total peripheral resistance by relaxing the vascular smooth muscle. Minoxidil, sodium nitroprusside are vasodilator substances. All these induce dilation of arterioles, causing a lowering of the SVR. Na nitroprusside is the only one that causes dilation of both arteries and veins, the other effect only arterial vessel. As a consequence it causes a dec in the cardiac output and has a more profound effect in decreasing the bp.

Glyceryl trinitrate can also be used in the treatment of hypertension and it acts as a venodilator, but also affects the smooth muscles reducing both venous return and peripheral resistance. It is used with hypertension related to surgery and post operative situations. Main side effects are hypotension, headache, peripheral oedema and allergic rash.

Centrally acting agents:

These act by stimulating the α_2 receptors situated presynaptically in the vasomotor center of the medulla and these are involved in inhibiting the release of noradrenaline from the adrenergic nerve terminals. Either there is a decrease in the SVR or cardiac output. Methyldopa is involved in reducing SVR whereas Clonidine is involved in reducing cardiac output. Methyldopa is like a prodrug. And is an analogue of L – dopa from which adrenalin, noradrenalin and dopamine are released, and it is converted into the false transmitter methylnoradrenaline.

Clonidine acts directly as a partial α_2 agonist.

Recommended combinations are:

1. A diuretic with a β – blocker or ACE inhibitor
2. Ca Channel blocker , with either a β – blocker or an ACE inhibitor.

Drugs used to promote tissue perfusion:

Angina pectoris – means chest pain.

Drugs used to relieve this are:

Peripheral vasodilators

Selective coronary dilators

Beta – adrenergic antagonists

Ca Channel Blockers

Their mode of action

Inc the secondary messenger

Blocking ca entry

Hyperpolarizing the cell membrane.

Peripheral vasodilators:

Act both on the arterial and veins to reduce the work load of the heart. They cause the dilation of the arteries as a result there is a dec in the peripheral resistance which the ventricles have to overcome to eject blood into the circulation. Venodilation results in there being a pool of blood and less blood is returned back and as a result less work has to be done by the heart.

Mainly are a group of nitrates such as glyceryl trinitrate, isosoride dinitrate, mononitrate.

The nitrate is absorbed by the endothelial cells and is converted into nitic oxide via the sulfhydryl dependent catalyst which increases the intracellular level of cGMP and in turn alters the availability of ca ions within the muscle cell. As a result there is dilation of the blood vessel. It more marked on the venous side. Common side effects are reflex tachycardia, hypotension, facial flushing, syncope and migraine like headache.

Coronary vasodilators: dipyridamole is used as a prophylactic agent to reduce the frequency of attacks and the requirement for glyceryl trinitrate treatment. It inhibits the phosphodiesterase which results in an inc in the secondary messenger cAMP as a result there is vasodilation of the coronary artery. It selectively causes vasodilation of the coronary vessels as a result there is an inc blood flow to the heart and an inc oxygen supply, it can worsen ischaemia in some cases. Adverse reactions are mild and include dizziness, headache, skin rashes and GI upset

B Blockers – reduce heart rate and workload of the heart.

Ca Channel blockers covered before... but it depends on which ca channel it affects.

Potassium Channel openers: Nicorandil is a derivative of nitrates. It relaxes the vascular smooth muscle of the veins. It opens the potassium channels and allows an efflux of potassium as a result of which it hyperpolarizes the membranes and in turn prevents the ca channel from opening. The unavailability of the ca produces arterial vasodilation. Common side effects are headache, facial flushing, nausea, vomiting, dizziness and weakness.

Anticoagulant, thrombolytics and antiplatelet drugs:

Anticoagulants: persons prone to blood – clots, it is possible to use drugs that interfere with normal blood coagulation processes and thus help to prevent thrombus formation. Over inhibition will lead to bleeding disorders. Blood clotting involves two procedures: the adherence of platelets to each other resulting in a platelet plug. The second being the actual process of blood clot itself due to fibrin formation. Since the second is the major cause of blood clot the anticoagulation treatment is geared towards the partial inhibition of this process. Heparin and Warfarin.

Heparin: is a polysachharide that occurs naturally in the lungs where its function is not known. Strong ionic compound which is lipophobic and hence cannot be given orally. It is given subcutaneously for slow action or iv for fast action. It enhances the action of the natural inhibitor of coagulation antithrombin III. At high doses leads to the inactivation of all the clotting factors but at low doses only Xa is affected. Bleeding is the only side effect and to counter this problem protamine sulfate is used. Since they are available as high mol wt heparin and this can

cause thrombocytopenia and hence we also get low mol wt heparin such as enoxaparin, dalteparin and these can also be used during pregnancy.

Warfarin: is the mainstay of the long term anticoagulant therapy and is a member of the coumarin group. It is structurally similar to vit k which is involved in the synthesis of prothrombin and other factors in the liver. The vit k is reduced since it acts as a coenzyme and needs to be oxidized into its active form before it can be reused again and this is done with the help of epoxide reductase. Warfarin inhibits this enzyme and hence prevent coagulation. Vit k in excess can serve as an antidote for warfarin toxicity. It takes time for its action since all the amount of active vit K has to be depleted and all the enzyme has to be inhibited by warfarin. It is almost devoid of adverse effect.

Drug – food interaction and drug - drug interaction should be monitored when taking warfarin as it is known to have either an overactivity or underactivity under the influence of certain foodstuff and other drugs.

Thrombolytic or fibrinolytic drugs:

A blood clot that is formed prevents the loss of body fluid and entry of outside material into the body but the clot itself undergoes dissolution at the site of injury once the tissue repair starts taking place. This process involves the bodies fibrinolytic process. The proenzyme plasminogen can be converted into plasmin and this degrades the fibrin present in the clot, this conversion takes place at the site of the clot and is due to the release of plasminogen activators from various cells. By using this mechanism and overstimulation of the release of plasminogen there can be dissolution of clots in the cases of thromboses and thus prevent the ischaemia in the blood – starved tissue.

Three types of drugs:

Streptokinase: is an enzyme prepared from β – haemolytic streptococci and is a potent activator of plasminogen. Without directly enzymatically cleaving

plasminogen into plasmin it acts by binding to plasminogen and this complex in turn acts on other molecules of plasminogen converting them into plasmin molecules. If there is an excess of the plasmin in the circulation it can cause a degradation of the clotting factor leading to an haemorrhagic episode. Since it is of a bacterial origin it can stimulate an immunoresponse.

Tissue Plasminogen Activator tpa:

Is of human origin and is made by recombinant DNA tech. it is clot specific and activates plasminogen that is within clots thus minimizing the haemorrhagic episodes. Should be given immediately after an MI and within six hours to be effective. Alteplase, tenecteplase and reteplase are the three forms of this enzyme.

Antiplatelet Drugs:

This is related to the formation of platelet plug. Platelets bind to the exposed collagen fibers and release various chemicals including the one called thromboxane. This inhibits the enzyme adenylate cyclase which is needed to make cyclic AMP. cAMP inhibits platelet adhesiveness and this is destroyed by the enzyme phosphodiesterase. Any drug that alters the amount of cAMP will have some effect on the platelet plug. Most pg's have this function but aspirin has the most because of its non – competitive action.

Aspirin: it is a member of the salicylates and is acetylsalicylic acid and the acetyl group react chemically with the enzyme cyclo – oxygenase which is needed for the synthesis of thromboxane. It is a non – competitive inhibitor of this enzyme and thus makes this enzyme completely inactive rendering the platelets functionless for the rest of their lifespan.

Diuretics

Are a group of drugs that promote water loss from the body into urine. They have a principal action at the level of nephrons. Some of the diuretics also act elsewhere in the body.

Loop Diuretics:

Furosemide, ethacrynic acid and bumetanide. These drugs act on the ascending limb of the loop of henle of the nephron. They inhibit the reabsorption of Na and Cl ions from the loop into the interstitial fluid. This results in the fluid to become very hypotonic as a result there is a high concentration of ions over here so water will flow thru the interstitial fluid and from there into the blood stream. By altering the permeability of the collecting duct good water control is achieved and this is done in the presence of an antidiuretic hormone ADH released from the posterior pituitary. A slight change in balance will upset the normal functioning of the kidney and a hypotonic interstitial fluid will result in diuresis. These diuretics have a high efficacy. Major adverse reaction is the loss of electrolyte from the body. Loss of K can lead to hypokalaemia and this turn can lead to cardiac dysrhythmias and death. K supplements need to be given and there needs to be an high intake of K in the diet.

Thiazides or thiazide like drugs: these act on the ascending loop of henle of the nephron. They dec Na reabsorption and as a result the fluid entering the collecting ducts is concentrated and hence less water is absorbed leading to diuresis. They have an effect on the peripheral artiole and this results in vasodilation. Adverse reaction sodium and K loss hence supplementation is required. Can cause hyperglycaemia hence care needs to be taken. Lactation can be suppressed. They contain a sulfonamide group hence persons allergic to this group should not be given this medication. Photosensitivity can also result.

K – sparing diuretics: these are not very powerful diuretics and hence are given in combination with either of the two above mentioned diuretics. There are two type aldosterone dependent and aldosterone independent.

Aldosterone antagonist - spironolactone – the mechanism of this is to inhibit the action of aldosterone on the distal convoluted tubule of the nephron. Aldosterone is the sodium retaining hormone that is secreted from the adrenal cortex. If it acts on the distal tubule then more Na is retained by the body and this will result in loss of K. If the aldosterone is blocked K is retained and Na is lost with a slight inc in diuresis. For every 2 molecules of K retained 3 molecules of Na is lost. It is this phenomenon that induces diuresis since more ions are lost than retained. It is of tremendous use in the treatment of Congestive heart Failure chf. The adverse reactions are hyperkalaemia and hyponatraemia. In men it can produce gynecomastia (breast development in men) due to its estrogenic effect.

Osmotic Diuresis: these work directly by interfering with osmosis. Any substance that enters the body in large quantities and is excreted via the kidney will lead to water being kept in the renal tubules and this will lead to water loss. This is due to the maintenance of high osmotic pressure in the tubules. The osmotic diuretics should be non – toxic, be excreted quickly and should not be reabsorbed from the glomerular filtrate. These substance have to be highly soluble in water and hence cannot be given orally and have to be given iv else will have a osmotic laxative effect. Adverse effects include dehydration and electrolyte imbalance. Commonly used in Mannitol. It is a sugar alcohol derived from mannose.

Drugs used to treat Cardiac insufficiency.

Myocardial Infarction predisposes a person to dysrhythmia and heart failure.

Heart failure is the impairment of the pumping ability of the heart. When the right side fails blood accumulates in the venal circulation causing organ congestion and peripheral tissue oedema. When the left side fails there is accumulation of blood in the pulmonary circulation resulting in pulmonary congestion and fluids in the lungs. When the left side of the heart is affected the condition is termed as congestive cardiac failure.

The current recommendation for treating heart failures is to treat with ACE inhibitors a diuretic and peripheral vasodilators and in some cases drugs that inc cardiac contractility are also used. There may also be a role for b – blockers in the long term management of this condition.

Inotropic Agents :

Cardiac Glycosides: Digoxin: they work by affecting the movement of ions in and out of the myocardial fibers, as well as altering the activity of ans. Ions most affected are Ca and Na. these drugs inhibit the action of the enzyme associated with the Na pump, ATPases and exchange between Na and Ca is impaired. Stores of Ca are released from the myocardial cells and the membranes become more permeable to this ion, as a result there are elevated levels of Ca. this result in stronger contraction of the heart since elevated levels of ca is associated with stronger contraction of the heart. Stronger myocardial contraction improves cardiac efficiency, boosting cardiac output. These enhance the psns stimulation of the heart and directly alter the responsiveness of the sinoatrial node. This results in dec heart rate and that is what we want since the sympathetic stimulation causes an inc in heart rate and can lead to an irregular pulse. The common adverse effects are forms of dysrhythmia such as tachycardia, fibrillations, ectopic depolarization and AV blockade. They trigger the CTZ zone in the brain leading to nausea and vomiting. Anorexia and diarrhea are consequences of direct GI irritation by these drugs. High levels of K reduce the effectiveness of these drugs. They have a relatively low margin of safety