Anti hypertensive drugs

Learning objectives

- Definition of hypertension
- factors regulating blood pressure
- non-pharmacological treatment of hypertension .
- classification of anti hypertensive drugs :-
- Diuretics
- centrally acting drugs
- calcium channels blockers
- angiotensin converting enzyme inhibitors ,angiotensin-2-receptors blockers
- beta blockers ,

Anti hypertensive drugs

- Hypertension is an increase in blood pressure -more than one occution-above the normal range (140/90mmHg)
- **Systolic blood pressure is the function of cardiac output**
- **(C.o.p.= stroke volume* Heart rate)**
- **Diastolic blood pressure is the function of the peripheral resistance of arterioles**
- **(B.pr. = C.O.P. * T.P.R.)**

Classification of hypertension

- According to etiology, the hypertension, is classified into:-

1- **Primary or essential or idiopathic hypertension (unknown cause >95%)**
2- **Secondary hypertension (< 5%)**

- **The predisposing factors of primary hypertension are**
- **positive family history (hereditary cause)**
- **smocking**
- **stress**
- **alcohol**

Causes of secondary hypertension

1) Renal causes include renal artery stenosis, glomerulonephritis, and parenchymal renal diseases
2) Endocrine causes such as Pheochromocytoma, Cushing's syndrome , hyperthyroidism ,hypothyroidism and Acromegaly
3) Vascular causes like coarctaion of aorta
4) Drugs ex. C.S.P., steroid,
5) Iatrogenic causes(made by doctor) like chronic treatment with steroids
6) Toxemia of pregnancy wither eclampsia or preeclampsia

Classification of hypertension

- According to severity, hypertension is classified into:-

1) Mild hypertension (diastolic pressure range 90-104mmHg)
2) Moderate hypertension (diastolic pressure range 105-115mmHg)
3) Severe hypertension (diastolic pressure is more than 115mmHg)
4) Malignant hypertension in which diastolic blood pressure more than 130mmHg in presence of papilledema with or without encephalopathy (infarcted or haemorrhage)and renal function impairment

Regulation of blood pressure

There are three mechanism to control blood pressure:

1) Baro-receptor control (functional in the acute setting –short term):

Blood pressure is controlled reflexively by stretch receptors in the carotid sinus and aortic body. When BP increase (hypertension),it increases stretching of the receptors, which will send impulses to the vasomotor centers in the brainstem, causing a reduce sympathetic drive and increase parasympathetic tone this will lead to peripheral vasodilatation ,bradycardia and decrease left ventricular contractility lead to decrease BP.

2)Renin-angiotensin –aldosterone system(intermediate term mechanism)

Renin is released from the juxta-glomerular apparatus in response to β-receptor stimulation, reduced afferent arteriolar stretching(reduce tubular sodium and water load into the PCT. Renin activates angiotensinogen into angiotensin l which is activated via the enzyme ACE into AT ll. this protein has many actions that lead to raising BP.

3) Renal mechanism of BP control: long term mechanism .The kidneys regulate BP over a wide range of fluid intake.

Management of hypertension

- Target BP<140/90mmHg
- Benefit of treatment to reduce incidence of complications
- Duration of treatment usually long life
- Strategies of hypertension treatment include

A. Non-pharmacological measures (individualization approach):

1- control diet (salt , fat)

2- Ideal body weight

3- Give up smoking and alcohol consumption reduce

4- Avoid stress

5- Regular exercises are important

B. Pharmacological measures:

Drugs that control hypertension act to modify the various factors controlling BP e.g. plasma volume, venous return, COP, HR,LV contractility, peripheral resistance

- monotherapy as possible is preferred

Classes of antihypertensive drugs

1- Diuretics (first line of treatment): include Thiazides, Loop diuretics and Potassium sparing diuretics

- **Thiazide diuretics**
- The main class of diuretics used in treatment of HT (mild or moderate HT with normal renal and cardiac function), include Chlorothiazide, Hydrochlorothiazide, Chlorthalidone and Metolazone
- Thiazides have the following actions
  - Direct vasodilating effect on blood vessels
  - Indirect acting through sodium depletion(hyponatremia), that lead to decrease responsiveness of blood vessels to endogenous vasoconstriction
  - Decrease volume of blood and extracellular fluid lead to decrease cardiac out put

- Side effects of Thiazide diuretics
- Hypokalemia, hyperglycemia, hyperuricemia, dyslipidemia, hypercalcemia, fatigue and hypotension

Diuretics

❖ Loop diuretics include

- Frusemide, Bumetanide, Ethacrynic acid and Torsemide, they are most potent diuretics, block sodium and water reabsorption from ascending limb of Henle, They are not used as primary drugs in the treatment of hypertension, but used in sever HT with edema due to HF,RF
- Side effects :- Hypokalemia, hypomagnesemia, hyperuricemia, and cause ototoxicity and nephrotoxicity

❖ Potassium-sparing diuretics include two groups

1- Aldosterone antagonist include Spironolactone and Eplerinone

2- Renal sodium channels blockers, that inhibit Na/K exchange in DCT, include Amiloride and Triameterene.

They used in treatment HT+ decrease potassium level.

They may cause hyperkalemia especially if used with ACEIs or ARBS

2- Sympatholytic drugs

Second line of hypertension treatment include:

- **β-blockers e.g. Carvedilol, Atenolol, Metoprolol, Bisoprolol, Esmolol**
- **α1- blockers e.g. Prazosin, Trimazosin, Doxazocin**
- **Mixed β and α- blockers e.g. Labetalol and Carvedilol**
- **Ganglionic blockers e.g. Trimethaphan**
- **These drugs act on**

- **Central level, Ganglionic level, Peripheral receptors level and nerve endings**
- **β-blockers widely used in treatment HT, act by inhibit or block sympathetic derive on heart lead to decrease HR and contractility, and also reduce renin release.**
- **Side effects: Brady cardia, impaired LV contractility, Peripheral vasoconstriction, worsening of asthma, Disturbance of lipid metabolism, insomnia, nightmares and erectile dysfunction and reduced libido ; they should be withdrawn gradually over a period of several weeks in patients with HT and IHD, (β-blocker withdrawal syndrome)**

3- Angiotensin Converting Enzyme Inhibitors(ACEIs)

ACEIs classified into

1- Sulfhydryl containing ACEIs e.g. Captopril

2- Carboxyl containing ACEIs e.g. Enalapril, Lisinopril

3- Phosphinyl containing ACEIs e.g. Fosinopril

MECHANISM OF ACTION :

They act on Renin- Angiotensin system prevent the activation of Angiotensin ll, through inhibit angiotensin converting enzyme (ACE), angiotensin ll act as:

1) Potent vasoconstrictor
2) Stimulates aldosterone secretion that cause sodium and water reabsorption
3) Stimulates cardiac and vascular smooth muscle cell growth lead to hypertrophy
4) Increase catecholamine formation and enhance sympathetic outflow
5) (ACE), has a role in bradykinin inactivation
6) So ACEIs lead to vasodilatation, they lower plasma aldosterone level, reducing salt and water reabsorption, impaired degradation of bradykinin which causes an increase in nitric oxide (NO) and prostacyclin, which are vasodilator substances, they reducing the intra glomerular pressure by prevent efferent arteriolar constriction, decrease cell growth and reduce vasomotor tone

Pharmacokinetic of ACEIs

- All ACEIs are orally bioavailable.
- Captopril and Lisinopril are active drugs, all other ACEIs are prodrugs, i.e. are converted by liver to an active metabolite(inactive for several hours after dosing).
- Their absorption from intestine is mostly effected by presence of food
- All ACEIs are excrete by kidney except Fosinopril, so it doesn't need dose modification in chronic renal diseases
- ACEIs are the only drugs which reduce after load and preload with little or no change in cardiac out put and heart rate
- In kidney, ACEIs increase renal blood flow and promote salt excretion

ACEIs

1- Captopril :

Is an ACEI causes arteiodilation and venodilation with little change in cardiac output and heart rate, so it is useful in treatment of hypertension associated with heart failure and in case of heart failure alone, has short half life (about 2 hrs.), so, it must be given 2-3 time/day, the fall in blood pressure can be rapid especially with short acting ACEIs including Captopril and low initial dose of these should be used in patients at risk(with renal problem and C.V.A.)

2- Enalapril:

Is a prodrug half life about 35 hrs. that is converted to the active form (Enalaprilat half life 10 hrs.),effective 24 control of blood pressure and given once –twice /day and unlike Captopril ,it has no sulfhydryl side chain , so doesn't cause cough

others Lisinopril its duration of action 24-30 hrs., so given once/day

CLINICAL USES OF ACEIs

1- hypertension with heart failure

2- Heart failure

3- Acute myocardial infarction(cause favorable myocardial remodeling)

4- Treatment of acute and chronic IHD

5- Hypertensive patients with renal impairment

6- Hypertensive diabetic patients(control of proteinuria in diabetic nephropathy)

7- Aortic regurgitation

8- Coarctaion of aorta

Side effects of ACEIs:-

1- Systemic Hypotension (first dose effect) and hyponatremia especially when a diuretic is also given

2-persist dry cough in 10-15% of patients, caused by accumulation of bradykinin in alveoli (especially sulfhydryl containing ACEIs)e.g. Captopril.

3- Hyperkalemia, so, they should be used cautiously in combination with k-sparing diuretics or potassium supplements

4- Urticaria and angioedema including ankle edema is rare, but serious side effect usually occurring in the first weeks of treatment due to high bradykinin level

5- Renal impairment , ACEIs cause reduction in renal function, however, they are the agents of choice in HT associated with renal impairment, as it preserves the remaining renal function

Contraindications of ACEIs:-

1- All ACEIs are contraindication in bilateral renal artery stenosis since they would induce renal insufficiency

2- ACEIs are absolutely contraindication in pregnancy due to teratogenic effect

3- Sever renal failure

4- Significant aortic stenosis

5- Hypertrophic and restrictive cardiomyopathy

4- Angiotensin ll receptor antagonists (All RA) or AT1 receptor antagonist

- Include Losartan, Valsartan, Telmisartan, and Candesartan
- they block the AT receptor type 1 and have almost the same action as ACEIs, they reduce the sympathetic tone leading to vasodilatation, reduce the peripheral vascular resistance, inhibit aldosterone release, and induce dilatation of the renal efferent arteriole causing a reduction in the amount of water and sodium reabsorption and thereby reducing plasma volume
- the only difference from ACEIs is that they don't inhibit bradykinin metabolism

Side effects:

Similar to ACEIs, with exception of a much less incidence of dry cough , ARBs are also teratogenic and should be avoided in pregnancy

5- Calcium channel blockers(CCBs)

These are a heterogeneous group of drugs belonging to various compounds

- Dihydropyridines:- Nifedipine, Amlodipine, Nicardipine, Felodipine
- Diphenylalkylamines: represented by Verapamil
- Benzothiazipines: Diltiazem
- **Mechanism of action:**

  Inhibits the passage of calcium through voltage- gated L- type channel lead to decrease intracellular calcium lead to relaxation
- CCBs have different mode of action according to group they belong to
- Dihydropyridines act mainly on vascular smooth muscles causing vasodilatation, they have little effect on heart rate
- Non- Dihydropyridines act mainly on cardiac conductive system and myocardial cells, inducing slowing of the heart rate and a negative inotropic effect(reduce contractility)

Calcium channel blockers(CCBs)

Pharmacokinetic:

All CCBs have short plasma half life except Amlodipine which can be administered once daily, sustained release preparations are available for the rest, so they can be used once or twice daily

Side effects

- Of Dihydropyridines include headache, flushing, leg edema, dizziness(postural hypotension) and gingival hypertrophy
- Of non- Dihydropyridines include bradycardia, atrio-ventricular block, and worsening of congestive heart failure, so they are contraindicated in any condition with impaired LV function
- CCBs are useful in hypertensive hypertrophic cardiomyopathy
- **Contraindications**: include
- heart failure or LV dysfunction
- significant aortic stenosis (negative inotropic effect lead to pulmonary edema)

6- Vasodilators

- ✓ **Include Hydralazine, Minoxidil, Diazoxide and sodium nitroprusside**
- ✓ (direct arterial and arteriolar smooth muscle relaxants)
- ✓ They reduce peripheral resistance leading to decrease DBP
- ✓ **Hydralazine:**
- ➢ Has a direct dilating action on arterioles with negligible effect on veins
- ➢ Metabolized in the liver by acetylation process, so in fast acetylation, decrease bioavailability and low antihypertensive effect
- ➢ Half life 2-4 hrs. and last longer time due to its binding to vascular tissues
- ➢ **Indications**
- ➢ I.V. infusion is useful in controlling hypertensive crisis in pregnancy(eclampsia)
- ➢ Oral therapy used in combination with β-blocker and thiazide.

6- Vasodilators

Side effects of Hydralazine

1. Headache ,flushing, dizziness
2. Reflex tachycardia (may precipitate angina)
3. SLE like syndrome

Minoxidil

Has higher efficacy than Hydralazine in the treatment sever HT , but its side effect, hirsutism, limited its use and using now as a topical solution for treatment of androgenic alopecia(baldness)

Diazoxide

Chemically similar to Thiazide, but without diuretic effect, it is potassium channel activator lead to vasodilatation, it is potent antihypertensive agent, used in hypertensive emergency associated with sever renal dysfunction or encephalopathy,, highly protein binding ,so must given rapidly, maximum effect within 4 minutes and last 4 hrs.

6- Vasodilators

Diazoxide side effects:-

- Sever hypotensive effect may lead to strock or angina
- Hyperglycemia ,hyperuricemia
- Increase sodium and water retention may lead to heart failure (i.v. Frusemide is often used)

Contraindication of Diazoxide

- Hypertensive crises with pulmonary edema
- Dissecting aortic aneurysm
- Coarctation of aorta
- Sever diabetes mellitus

6- Vasodilators

Sodium nitroprusside

It is potent ,rapid acting I.v. antihypertensive agent, given by infusion pump, its effect is immediate and last for 1-5 minutes, it dilates both arterioles and veins, it is rapidly metabolized by up take into RBCs and liberation of cyanide that converting normal Hb into met Hb, and nitric oxide(NO)release

INDICATIONS:-

- ❑ Emergency hypertension
- ❑ Controlled hypertension during surgery
- ❑ Refractory heart failure

Contraindications:-

- ❖ Hepatic failure
- ❖ Sever renal dysfunction

7-Centrally acting antihypertensive drugs

Include Clonidine and Methyldopa

Clonidine

It act by stimulating central sympathetic α-2 receptors in the vasomotor center in the CNS, this stimulation lead to inhibition of the peripheral sympathetic tone , reducing peripheral vascular resistance without any effect on the kidneys, it is available in oral and transdermal forms

Side effects:-

Sedation, constipation, dry mouth, abrupt cessation of treatment lead to rise of blood pressure (rebound phenomenon)

Methyl dopa:-

It is stimulating the central sympathetic α-2 receptors, it is converted in the CNS into methyl norepinephrine(false transmitter), it reduce central sympathetic flow , it is safe in pregnancy, which is the major indication of the drug

Side effects:- depression, nightmares, gynecomastia, galactorrhea, male sexual dysfunction and positive Coombs test with haemolytic anemia