ANTIHYPERTENSIVE DRUGS

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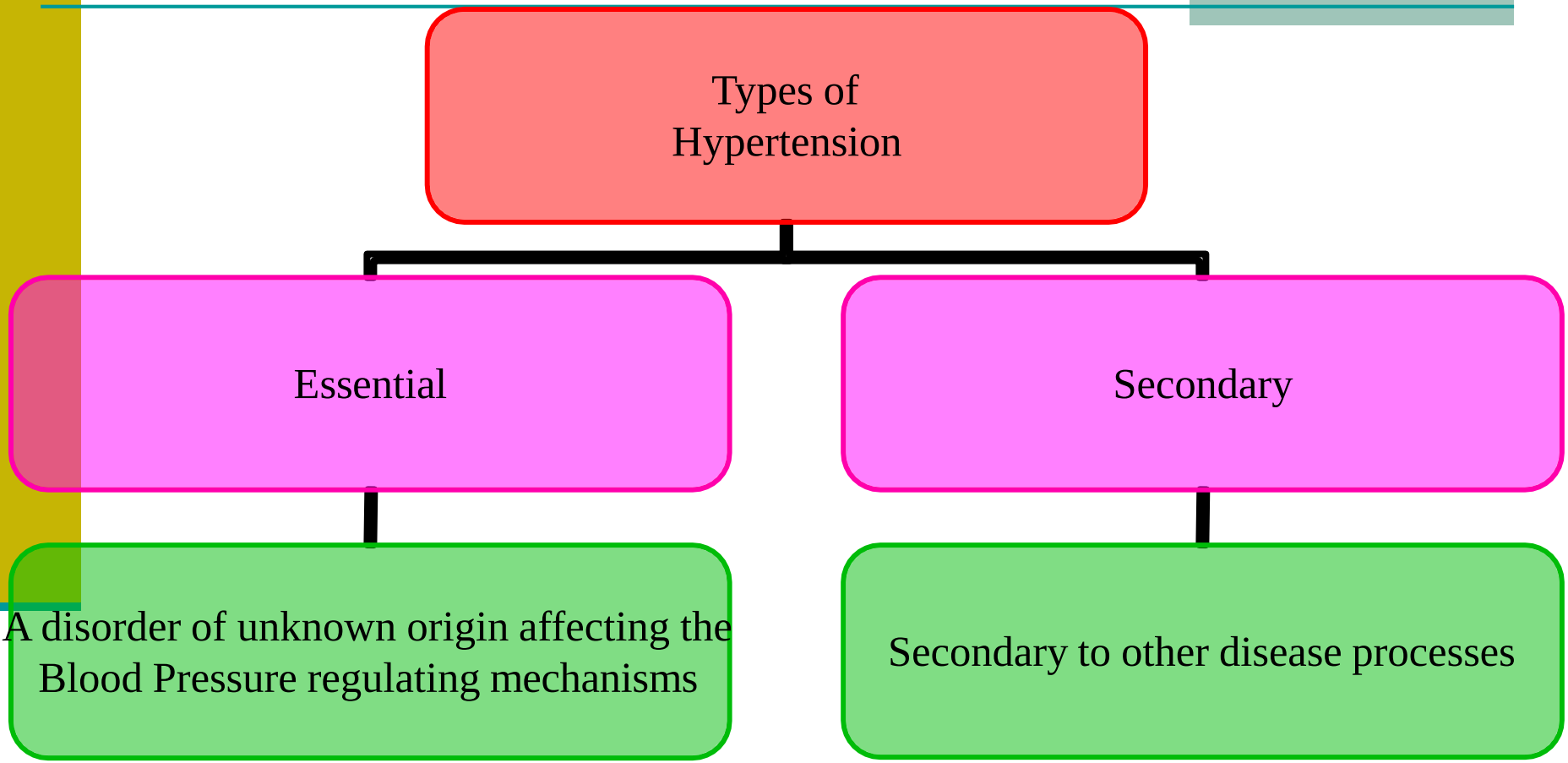
Introduction

- Hypertension is a very common disorder particularly past middle age.

- Hypertension is defined as a **BP more than 140mm Hg systolic and 90mm Hg diastolic.** (Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure 7 guidelines).

Introduction



Classification of Hypertension on The Basis of Blood Pressure

Systolic/Diastolic Pressure (mm Hg)	Category
< 120/80	Normal
120–135/80–89	Prehypertension
≥ 140/90	Hypertension
140–159/90–99	Stage 1
≥ 160/100	Stage 2

From the Joint National Committee on prevention, detection, evaluation, and treatment of high blood pressure. JAMA 2003;289:2560.

Normal Regulation of Blood Pressure

According to the hydraulic equation, arterial blood pressure (BP) is directly proportionate to the product of the blood flow (cardiac output, CO) and the resistance to passage of blood through precapillary arterioles (peripheral vascular resistance, PVR)

- **BP = CO × PVR**

Introduction

Outcomes of Hypertension :-

- **Atherosclerosis**
- **Ischemic heart disease & cerebrovascular accidents (CVA)**
- **Nephropathy**
- **Congestive heart failure**

"***Hence early detection &treatment of htn with antihypertensive drugs is very important***"

Normal Blood Pressure Regulation

1. Blood Pressure = Cardiac output (CO) X TPR.
   Physiologically CO and PVR is maintained by **arterioles , postcapillary venules & Heart .**

2. Baroreflex : **Baroreceptors** regulate BP. Central sympathetic neurones in vasomotor area are tonically active. When there is stretch in the vessel wall brought about by rise in pressure, baroreceptor stimulation occurs and inhibits sympathetic discharge. When there is fall in BP, there is reduction in stretch leading to increased baroreceptor activity leading to increase in TPR and CO thereby restoring normal blood pressure.

3. Renin-angiotensin- aldosterone system **(RAAS**)(role of kidney)

4. Local agents **like Nitric oxide**

- **All antihypertensives act via interfering with one or more of the normal mechanisms**

Classification of Antihypertensive Drugs

1. **Diuretics:**
   - Thiazides: Hydrochlorothiazide, Chlorthalidone, Indapamide
   - High ceiling: Furosemide
   - K+ sparing: Spironolactone, Triamterene, Amiloride

1. **Angiotensin-converting Enzyme (ACE) inhibitors:**
   - Captopril, Lisinopril., Enalapril, Ramipril , Fosinopril

2. **Angiotensin (AT1 receptor) blockers:**
   - Losartan, Candesartan, Valsartan, Telmisartan

4. **Direct renin inhibitor**

   Aliskiren

Classification of Antihypertensive Drugs

5. Calcium Channel Blockers (CCB):

- Verapamil, Diltiazem, Nifedipine, Amlodipine,

6. ß-adrenergic blockers:

- **Non selective:** Propranolol
- **Cardioselective: Metoprolol** , atenolol

7. ß and α – adrenergic blockers:

- Labetolol, carvedilol

8. α – adrenergic blockers:

- Prazosin, terazosin, doxazosin, phenoxybenzamine , phentolamine

9. Centrally acting:

- Clonidine, methyldopa

Classification of Antihypertensive Drugs

10. Vasodilators:

- Arteriolar : Hydralazine, Minoxidil, Diazoxide
- Arteriolar + venous: Sodium Nitroprusside

*Pnemonic : **ABCD***

A (ACEI, ARBs, alpha blockers) B(beta blockers)C (CCB, centrally acting) D (Diuretics, direct renin inhibitors, dilators)

Each group of drugs will be discussed under the following headings

- Examples of drugs under each group
- Mechanism of antihypertensive action
- Desirable properties as antihypertensives
- Drawbacks as antihypertensives
- Current status in treatment of hypertension

Diuretics

Examples :

- Thiazides: Hydrochlorothiazide, Chlorthalidone, Indapamide
- High ceiling: Furosemide
- K+ sparing: Spironolactone, Triamterene, Amiloride

Diuretics

- **Mechanism of antihypertensive action: (Thiazides)**

Act on Kidneys to increase excretion of Na and H2O → decrease in blood volume →decrease in COP & hence decrease in BP.

- After 4 - 6 weeks, compensatory mechanisms operate to regain Na+ balance, plasma volume and Cardiac output but BP remains low. Why?
- Answer: Even after the compensatory mechanisms, there exists a small deficit of Na+ in the vessel wall. This Na deficit reduces stiffness of vessel wall leading to vasodilation . This leads to decrease in TPR and fall in BP.
- So, the initial fall in BP due to thiazides is due to fall in COP but fall in BP is sustained due to fall in TPR.

Diuretics

Mechanism of antihypertensive action (high ceiling diuretics)

Fall in BP is dependent only on reduction in plasma volume & Cardiac output (similar to the initial fall in BP due to thiazides) but unlike thiazides the Na deficit is not persistent due to short action of high ceiling diuretics . Hence no fall in t.p.r and no sustenance of BP fall.

Diuretics

Desirable properties of Diuretics as antihypertensives

- Once a day dosing
- No fluid retention
- No tolerance development to antihypertensive action
- Low incidence of postural hypotension
- Effective in isolated systemic hypertension
- Less risk of fractures in elderly (hypocalciuric action of thiazides)
- Low cost

Diuretics

Drawbacks of Diuretics as antihypertensives

- Hypokalaemia – muscle pain and fatigue
- Hyperglycemia
- Hyperlipidemia
- Hyperuricaemia
- Sudden cardiac death – tosades de pointes due to hypokalemia

All the above adverse effects occurr at higher doses of thiazides (50 – 100 mg per day). These adverse effects are minimal with low doses (12.5 to 25 mg). So, low doses of Thiazides are used as antihypertensives now.

Diuretics

Current status

- Thiazides are mild antihypertensives, cause fall of abt 10mm Hg in BP. Alone they are used only in **mild HTN (stage 1 HTN)**. Low dose of thiazide therapy is used preferably with a potassium sparing diuretic as first choice in **elderly**.

- They **prevent tolerance** to other antihypertensives. Can be used as combination in any grade of HTN.

Indapamide : modified thiazide with minimal side effects

It has very mild diuretic action and is used mainly as antihypertensive and not as diuretic.

Diuretics

Loop diuretics

Cause more fluid & electrolyte imbalance. They are indicated in HTN only if it is complicated by:-

- Chronic renal failure
- Refractory CHF
- Resistance to thiazides
- Marked fluid retention.

K+ sparing diuretics

Used only in conjunction with Thiazides to prevent **K+ loss & to supplement their antihypertensive action.**

Angiotensin Converting Enzyme (ACE) Inhibitors

Examples :-

Captopril, Lisinopril., Enalapril, Ramipril , Fosinopril

Mechanism of antihypertensive action

Inhibit the Renin Angiotensin Aldosterone system (RAAS).

WHAT IS RAAS???

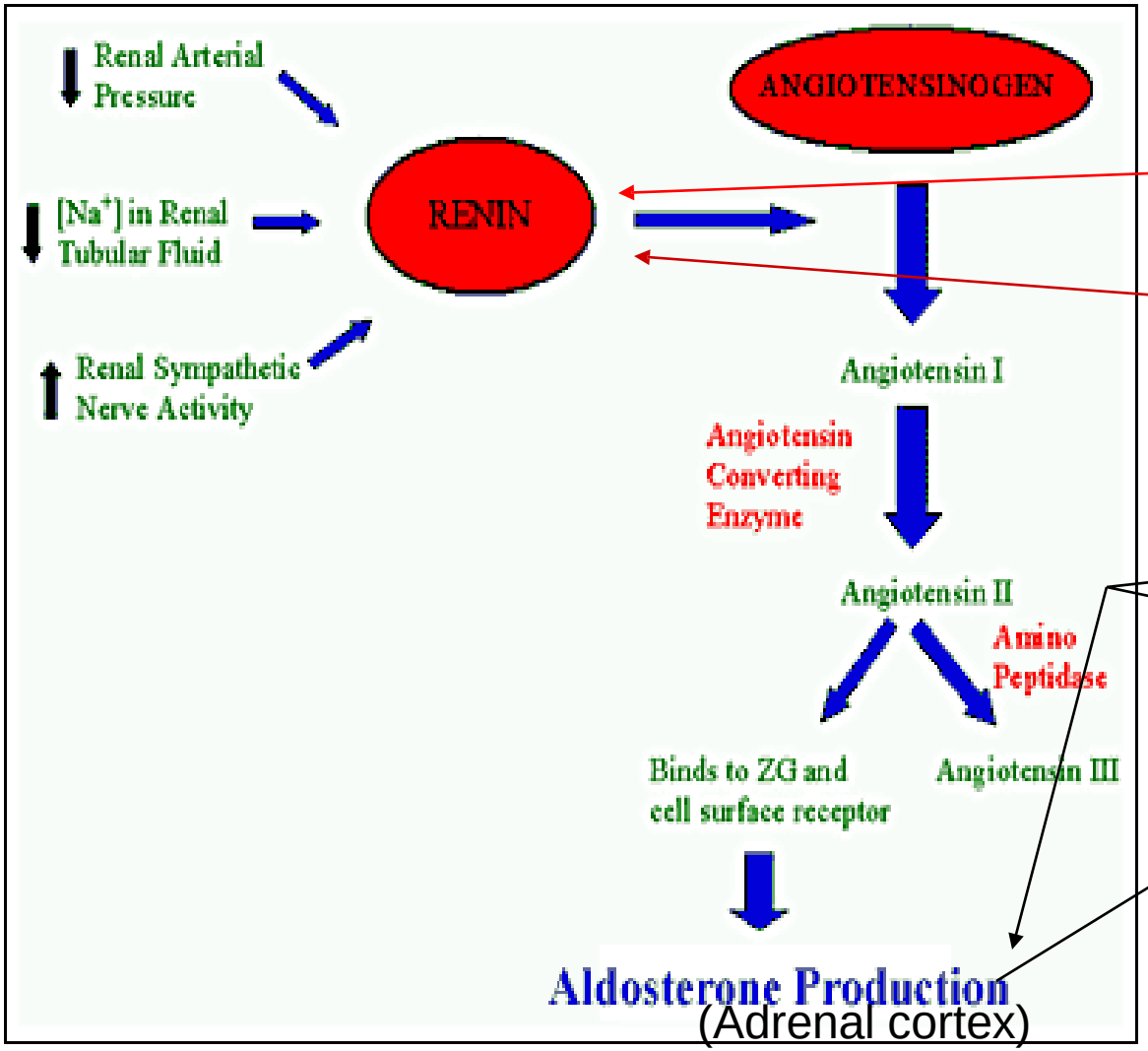
Next slide

RAAS

- **Renin** is produced by JG cells of kidney in response to
  - Fall in BP or blood volume
  - Decrease Na+ in macula densa
- Renin acts on a plasma protein **Angiotensinogen** to convert it to **Angiotensin-I**
- **Angiotensin-I** is rapidly converted to **Angiotensin-II** by ACE (present in luminal surface of vascular endothelium)
- **Angiotensin-II** is degraded by peptidases to produce **Angiotensin-III**

- Angiotensin II causes vasoconstriction (increased TPR) leading to rise in diastolic BP.
- Both **Angiotensin-II** and **Angiotensin-III** stimulates **Aldosterone** secretion from Adrenal Cortex . Aldosterone promotes Na+ & water reabsorption by the kidneys leading to increased blood volume & increased COP & systolic BP.

RAAS - Diagram



ACE inhibitors

MOA : **Inhibit synthesis of Angiotensin II by inhibiting ACE –> decrease in (tpr) and blood volume→fall in diastolic and systolic BP.**

ACE inhibitors

Desirable properties of ACEI as anti-hypertensive

- No postural hypotension
- Not much electrolyte imbalance
- Renal perfusion well maintained
- **Reverses the ventricular hypertrophy**
- No hyperuricemia
- No deleterious effect on plasma lipid profile
- No rebound hypertension
- Only minimal worsening of quality of life like general wellbeing, sleep and work performance.

ACE inhibitors

Drawbacks/ adverse effects

- Cough – persistent brassy cough due to inhibition of bradykinin breakdown in lungs
- Hyperkalemia (in renal failure patients, those with K+ sparing diuretics, NSAID and beta blockers (routine check of K+ level))
- First dose Hypotension – sharp fall may occur
- Angioedema: swelling of lips, mouth, nose etc.
- Rashes, urticaria
- Dysgeusia: loss or alteration of taste
- Foetopathic: hypoplasia of organs, growth retardation etc
- Neutropenia
- Proteinuria
- Acute renal failure (occurs in patients with bilateral renal artery stenosis)

ACE inhibitors

Current status

- 1st line antihypertensive Drug
- Used in relatively **young patients**
- Most appropriate antihypertensives in patients with:-
  Diabetes,
  Chronic kidney disease,
  CHF
  Left ventricular hypertrophy,
  Angina, post MI, stroke
  Dyslipidemia,
  Gout

Avoid in : Pregnancy, bilateral renal artery stenosis, hypersensitivity , hyperkalaemia , Preexisting dry cough

ACE inhibitors (2 important ones)

Captopril

- Sulfhydryl containing dipeptide.
- Not a prodrug. Has drawbacks mentioned earlier
- Half life: 2 Hrs, multiple doses

Enalapril

- Prodrug – converted to enalaprilate
- Advantages over captopril:
  - More potent
  - Longer duration of action-once daily dose
  - Absorption not affected by food
  - Rash and loss of taste are less frequent
  - Slower onset of action, hence first dose hypotension less marked

ACE inhibitors – other uses (to be discussed under ACE inhibitors chapter)

- Congestive Heart Failure
- Myocardial Infarction
- Prophylaxis of high CVS risk subjects
- Diabetic Nephropathy
- Schleroderma crisis

Angiotensin Receptor Blockers (ARBs)

Examples

Losartan, Candesartan, Valsartan,Telmisartan

Mechanism of antihypertensive action

Angiotensin Receptors (AT1 & AT2) are present on target cells. Most of the physiological actions of angiotensin are mediated via **AT1 receptor.**

- ARBs are competitive antagonists and inverse agonist of AT1 receptor. Blocks all the actions of A-II mediated by AT1 like vasoconstriction, aldosterone release and renal actions of salt & water reabsorption.

ARBs

Current status of ARBs

Similar to ACEI **BUT** theoretical superiority over ACEIs is claimed due to following reasons:

- Cough is rare – no interference with bradykinin degradation.
- Complete inhibition of AT1 & action of angiotensin II is fully blocked– (In case of ACEI, Angiotensin II formed by other mechanisms not involving ACE can act on AT1 reeptor & produce the effects)
- AT1 blockade results in indirect activation of AT2 – vasodilatation (additional benefit)
- Rare 1st dose hypotension
- Low dysgeusia & angioedema

Fetopathic like ACEI & hence should not be used in pregnancy.

Direct renin inhibitor-Aliskiren

- Inhibits production of Angiotensin I & II.
- Equally effective as ACEI & ARBs.
- Since experience with it is limited, so it is used only as a **second line antihypertensive** when more established ACEI & ARBs cannot be used.

Beta blockers

Examples

- **Non selective: Propranolol**
- **Cardioselective: Metoprolol**, **Atenolol**

Mechanism of antihypertensive action

- Decreases heart rate, contractility, conduction velocity, cardiac output (inverse agonist on β1). Total peripheral resistance increases initially.
- Initial phase : COP decreases (systolic BP decreases), t.p.r increases (diastolic BP increases) →overall little BP change.
- With prolonged use resistance vessels adapt to decreased COP so that t.p.r decreases→ both systolic & diastolic BP decrease

Beta blockers

Desirable properties as antihypertensives

- No postural hypotension
- No salt and water retention
- Low incidence of side effects
- Low cost
- Once a day regime

Drawbacks of non selective beta blockers:-

- Fatigue, lethargy (low CO?)– decreased work capacity
- Bradycardia
- Loss of libido – impotence
- Cognitive defects – forgetfulness
- Worsening of carbohydrate tolerance, lipid profile, PVD, asthma.
- Sudden withdrawal—chance of rebound HTN, precipitation of MI or angina

Beta blockers

Advantages of cardio-selective beta blockers over non-selective beta blockers:

- Safer in asthmatics (no bronchoconstriction)
- Safer in diabetes (no interference with hypoglycemia induced glycogenolysis)
- Less worsening of PVD
- Lipid profile-less deterioration

Beta blockers

Current status:

- As first line drugs cardioselective beta blockers alone in mild/moderate HTN
  - Action maintained over 24hrs
- Preferred in:-
- Young non-obese hypertensives those with coexisting anxiety, migraine, tachycardia & those with IHD
- For preventing sudden cardiac death in Post MI patients
- In stable heart failure along with ACEI
- Not preferred in old

Alpha blockers

- **Examples**

  Non selective alpha blockers (Phenoxybenzamine, Phentolamine) not used in chronic essential hypertension but used in Pheochromocytoma.

  Specific alpha-1 blockers like prazosin, terazosin and doxazosine are used in HTN treatment

- **<u>Mechanism of antihypertensive action</u>**

Blockade of vasoconstrictor α receptors

- pooling of blood in capacitance vessels→decreased venous return & decreased COP→ fall in BP

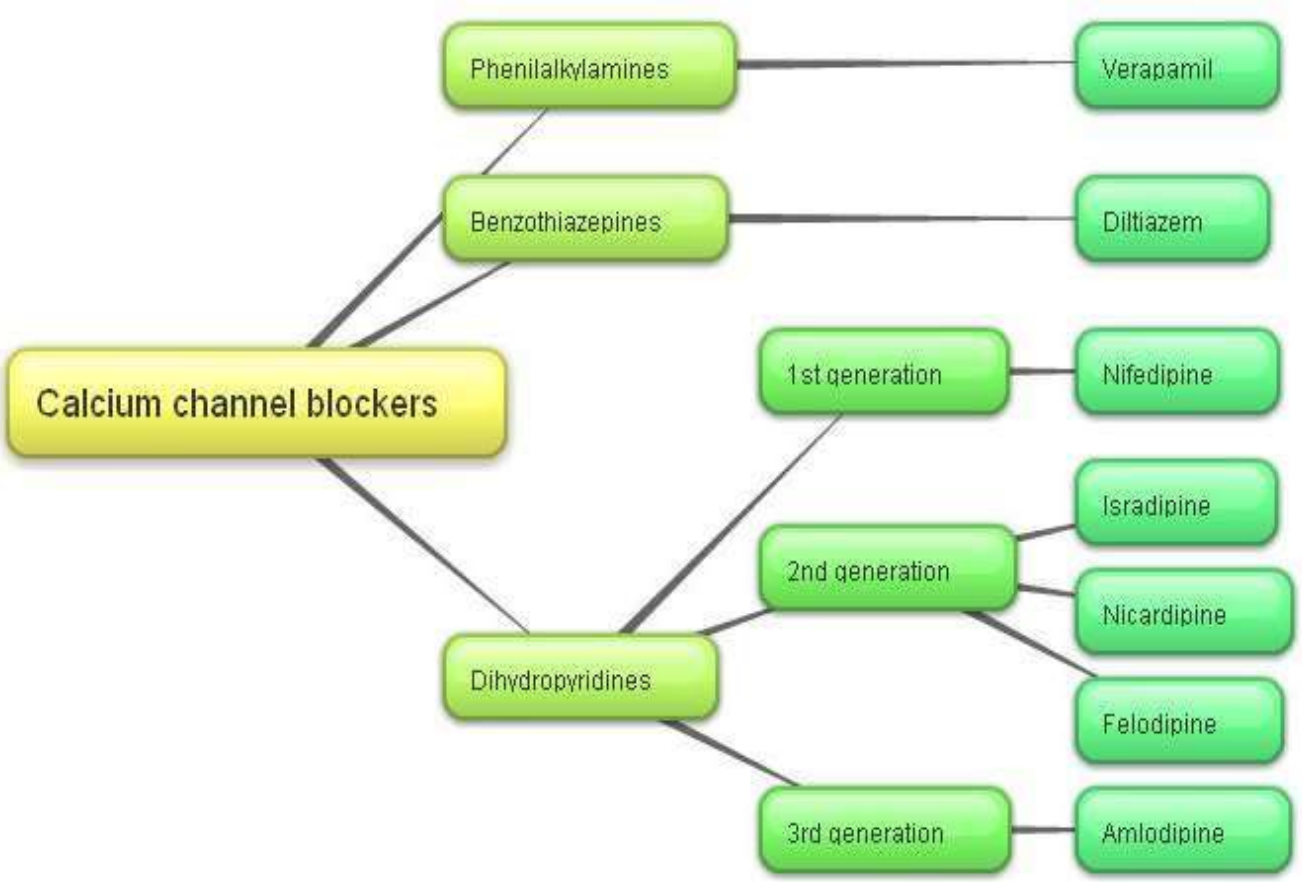
Alpha blockers

- **Adverse effects:**
  - postural hypotension
  - salt and water retention
  - Nasal stuffiness
  - Miosis
  - failure of ejaculation in males
- **Current status:**
  - But not used as first line agent,
  - May be added to diuretics + beta blockers if target bp is not achieved with their use alone.

Alpha + beta blockers

- Labetalol used IV for rapid BP reduction. Orally used for severe HTN.
- Carvedilol used as antihypertensive as well as in CHF.

Calcium Channel Blockers - Classification



Calcium Channel Blockers

Mechanism of antihypertensive action

- Three types of Ca+ channels in smooth muscles – Voltage sensitive, receptor operated and leak channel
- Voltage sensitive are again 3 types – L-Type, T-Type and N-Type
- Normally, L-Type of channels admit Ca+ and causes depolarization – excitation-contraction coupling through phosphorylation of myosin light chain – contraction of vascular smooth muscle –vasoconstriction-- elevation of BP
- **CCBs block L-Type channel resulting in :-**
  - Smooth Muscle relaxation
  - Negative chronotropic, ionotropic effects on heart.
- **DHPs** have highest smooth muscle relaxation and vasodilator action followed by verapamil and diltiazem. Hence DHPs are the CCBs used in HTN.

Calcium Channel Blockers

Desirable properties

- Do not compromise haemodynamics – no impairment of work capacity
- No deleterious effect on lipid profile, uric acid or electrolyte balance.
- Can be given to asthma, angina and PVD patients
- No renal and male sexual function impairment
- **No adverse fetal effects and can be given in pregnancy**
- Minimal effect on quality of life

Calcium Channel Blockers

Drawbacks

- Worsen GERD
- Negative chronotropic effect can worsen Conduction defects
- Worsen BHP & bladder voiding difficulty in males

Calcium Channel Blockers

Current status

- Used as 1st line by many because of excellent tolerability and high efficacy.
- Preferred in elderly/asthma/COPD/PVD/ stroke/DM/pregnant/isolated systolic HTN
- To be avoided in:-
  - Myocardial inadequacy, CHF
  - Conduction defects
  - Receiving beta blockers
  - IHD, post MI cases.
  - Enlarged prostate
  - GERD

Vasodilators

Hydralazine

- Directly acting vasodilator
- **MOA**: hydralazine causes NO release – relaxation of vascular smooth muscle – fall in BP.
- Uses: 1) Moderate hypertension when 1st line fails
  2) Hypertension in Pregnancy

Minoxidil

Relaxes smooth muscle & relaxes arterioles.

Used only in life threatening HTN & topically in alopecia

Sodium Nitroprusside

- Rapidly acting vasodilator (both arteriolar & venous)
- MOA: RBCs convert nitroprusside to NO (enzymatically) & non enzymatically by glutathione to NO & CN- –..>NO causes vasodilation of both resistance (arterioles) and capacitance vessels (veins) and reduces t.p.r and CO (decrease in venous return)

- Uses: **Hypertensive Emergencies**
- Adverse effects: Palpitation, pain abdomen, disorientation, psychosis, weakness and lactic acidosis.
- Psychosis is due to CN- formation

Centrally acting Drugs

- Alpha-Methyl dopa: (Alpha methyl analogue of DOPA) - a prodrug
  - MOA:Gets converted to alpha methyl Noradrenaline.

    which acts on alpha-2 receptors in brain and causes inhibition of adrenergic discharge – fall in BP
  - Only used therapeutically now **in Hypertension during pregnancy.**

- Clonidine: Agonist of central alpha-2 receptor
  - Not frequently used now because of tolerance and withdrawal hypertension

THANK YOU