Antihypertensive Drugs

CARDIOVASCULAR DRUGS

ACE INHIBITORS, ANGIONTENSIN II-RECEPTOR BLOCKERS, VASODILATORS

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ANTI-HYPERTENSIVE DRUGS

"THESE ARE THE DRUGS USED TO LOWER THE INCREASED BLOOD PRESSURE"

HYPERTENSION:

THE JNC-VII AND WHO-ISH GUIDELINES 2003 HAVE DEFINED:

WHEN SYSTOLIC BP EXCEEDS MORE THAN: 140 mm Hg &

DIASTOLIC BP EXCEEDS MORE THAN: 90mm Hg

is said to be ***HYPERTENSION.***

JNC-VIII -CLASSIFICATION OF HYPERTENSION:

- NORMAL (SBP\DBP) :<120|80
- PREHYPERTENSION : 120-139|80-89
- STAGE1 HYPERTENSION : 140-159|90-99
- STAGE2 HYPERTENSION : >160|>100

CLASSIFICATION:

DIURETICS:

- HYDROCHLOROTHIAZIDE
- CHLOROTHALIDONE
- INDAPAMIDE
- SPIRANOLACTONE
- AMILORIDE

ACE INHIBITORS:

- CAPTOPRIL
- ENALAPRIL
- LISINOPRIL
- RAMIPRIL
- FOSINOPRIL

ANGIOTENSIN (AT RECEPTOR) BLOCKERS

- LOSARTON
- TELMISARTAN
- VALSARTAN

CALCIUM CHANNEL BLOCKER:

- VEERAPAMIL
- DILTIAZEM
- NIFIDIPINE
- FELODIPINE
- AMLODIPINE
- LACIDIPINE

B-ADRENERGIC BLOCKER:

- PROPRONOLOL
- METOPROLOL
- ATENOLOL

β+α ADRENERGIC BLOCKERS:

- LABETALOL
- CARNEDILOL

- α- ADRENERGIC BLOCKERS:
  - PPRAZOSIN
  - DOXAZOSIN
  - TERAZOSIN
  - PHENTOLAMINE
  - PHENOXY BENZAMINE
- CENTRAL SYMPATHOLYTICS:
  - CLONIDINE
  - METHYLDOPA
- VASODIALATORS:
  - ARTERIOLAR HYDRALAZINE
  - ARTERIOLAR+VENOUS SODIUM NITROPRUSSIDE

DIURETICS:

- Standard antihypertensive drug - over the past 4 decades
- They *do not lower the BP in normo tensive*
- Very safe, inexpensive
- Effective in *preventing STROKE,MI,CHF*
- Diuretics are superior to Beeta Blockers in treatment of hypertensive in older adults

THIAZIDES:

DIURETICS

↓

REDUCES PLASMA & E.C.F VOLUME BY 5-15%

↓

DECREASED CARDIAC OUTPUT

↓

LOWER THE BP BY INCREASING SODIUM & WATER EXCRETION

LOOP DIURETICS:

- Used in patients who have not responded to thiazides or other diuretics
- Its weaker than thiazides

THEY REDUCE PLASMA VOLUME & CARDIAC OUTPUT BY INCREASING THE EXCRETION OF SODIUM & WATER

↓

FALL IN BP

POTASSIUM SPARING DIURETICS:

- Used in conjugation with thiazide diuretics,
- Act by preventing K^+ loss.

ACE INHIBITORS:

- Is the first choice drug in all types of hypertension
- When used alone control hypertension in -50% patients
- ACE INHIBITORS + DIURETICS/β- BLOCKER controls hypertension in 90% patients

WHEN BLOOD FLOW REDUCED IN KIDNEY

↓ Secretes

RENIN

↓

ANGIOTENSINOGEN →ANGIOTENSIN – 1

↓

ANGIOTENSIN – 2

↓

VASO CONSTRICTION & BREAKDOWN OF BRADYKININ (No accumulation of it - No dry cough)

ACE INHIBITORS

↓

BLOCKING THE CONVERSION OF ANGIOTENSIN-I TO ANGIOTENSIN-II

↓

VASODILATATION

↓

DECREASE IN THE HYPERTENSION (Decrease the break down of Bradykinin)

↓

Accumulation of bradykinin in body – Dry cough

PHARMACOKINETICS:

- About 70% of orally administered captopril is absorbed.
- Presence of food in stomach reduces its bioavailability.
- Penetration in brain is poor. It is partly metabolized and partly excreted unchanged in urine.
- The plasma t½ is ~2 hours,
- Actions last for 6–12 hours.

ADR:

- Fever
- Hyperkelemia
- Skin rash
- Hypotension

USES:

- Hypertension in young people's
- Effective in management of patient with chronic heart failure

ANGIOTENSIN RECEPTOR BLOCKERS:

– Eg: LOSARTON, TELMISARTAN, VALSARTAN

- The ARBs are alternatives to the ACE inhibitors.
- These drugs act by blocking the AT1 receptors
- They lowering blood pressure and decreasing salt and water retention
- ARBs do not increase bradykinin levels.
- They may be Used as first-line agents for the treatment of hypertension, especially in patients with a compelling indication of diabetes, heart failure, or chronic kidney disease

MACHANISM OF ACTION:

LOSARTON

↓

BLOCKING THE ANGIOTENSIN-I (AT-I) RECEPTOR

↓

PREVENTS THE BINDING OF ANGIOTENSIN-II TO AT-I RECEPTOR

↓

VASODILATATION

↓

DECREASE IN THE BLOOD PRESSURE

PHARMACOKINETICS:

- *Oral absorption of losartan* is not affected by food,
- bioavailability is only 33% due to first pass metabolism.
- It is partially carboxylated in liver to an active metabolite
- After oral ingestion peak plasma levels are attained at 1 hr
- They are 98% plasma protein bound,
- Excreted by the kidney.
- Dose should be reduced in presence of hepatic dysfunction.

ADR:

- Hypotension
- hyperkalemia,
- Headache,
- dizziness,
- weakness

CALCIUM CHANNEL BLOCKERS:

- Calcium channel blockers (CCBs) are another class of first line antihypertensive drugs.
- **VEERAPAMIL, DILTIAZEM, NIFIDIPINE**
  - **FELODIPINE**
  - **AMLODIPINE**
  - **LACIDIPINE**

CALCIUM CHANNELS

- Three types of Ca2+ channels have been described in smooth muscles
- (a) *Voltage sensitive channel* ***Activated when membrane*** potential drops to around –40 mV or lower.
  - L-type , T-type, N-type
- (b) *Receptor operated channel*
- (c) *Leak channel*
- Only the voltage sensitive L-type channels are blocked by the CCBs.

INWARD MOVEMENT OF Ca2+
MOVEMENT THROUGH 'L' TYPE VOLTAGE SENSITIVE CALCIUM CHANNELS

↓

THESE CALCIUM IONS TRIGGERS THE RELEASE OF MORE CALCIUM FROM INTRA CELLULAR STORES

↓

PHOSPHORYLATION OF MYOSIN LIGHT CHAIN IN THE MUSCLES

↓

CONTRACTION OF THE MUSCLE

CALCIUM CHANNEL BLOCKERS

↓

THROUGH 'L' TYPE VOLTAGE SENSITIVE CALCIUM CHANNELS

↓

PREVENTS THE ENTRY OF Ca2+ IONS IN TO THE MUSCLE

↓

DECREASE THE AVAILABILITY OF INTRA CELLULAR Ca2+ IONS

↓

PREVENTS THE PHOSPHORYLATION OF MYOSIN LIGHT CHAIN IN THE MUSCLES

↓

PREVENTS THE CONTACTION OF THE MUSCLE

↓

RELAXATION

Markedly relax arterioles , having mild effect on veins, extra vascular smooth muscle is also relaxed

VERAPAMIL:

- It *dilates arterioles* and has some α adrenergic blocking activity— *decreases t.p.r.*
- BP is only *modestly lowered.*
- The HR generally decreases,
- Coronary flow is increased.

PHARMACOKINETICS:

- Most of these agents have short half-lives (3 to 8 hours) ON oral dose.
- Sustained-release preparations are available and permit once-daily dosing.
- Amlodipine has a very long half-life and does not require a sustained-release formulation.

ADR:

- Nausea,
- constipation
- Bradycardia
- flushing,
- headache
- ankle edema

USES:

- CCBs may be used as an initial therapy or as add-on therapy.
- They are useful in the treatment of hypertensive patients who also have asthma, diabetes, and/or peripheral vascular disease.

β-ADRENERGIC BLOCKERS

Eg:PROPRONOLOL, METOPROLOL, ATENOLOL

- They are mild antihypertensives
- do not significantly lower BP in normotensives.
- Additional BP lowering may be obtained when combined with other drugs.
- Patient's acceptability of a β1 selective hydrophilic drug like atenolol is better than that of propranolol.
- Propronolol act by blocking the β receptors there by ↓ Heart rate, force of contraction & cardic output.

PHARMACOKINETICS

- The β-blockers are orally active for the treatment of hypertension.
- Propranolol undergoes extensive and highly variable first-pass metabolism.
- Oral β-blockers may take several weeks to develop their full effects.
- Esmolol, metoprolol, and propranolol are available in intra- venous formulations.

Adverse effects:

- bradycardia,
- hypotension,
- fatigue,
- lethargy,
- insomnia

THERAPEUTIC USES:

- Used in hypertensive patients with concomitant heart disease, such atrial fibrillation, previous myocardial infarction, angina pectoris, and chronic heart failure.
- Should not be used in asthma, second- and third-degree heart block, and severe peripheral vascular disease.

- **α- ADRENERGIC BLOCKERS:**
  - **PRAZOSIN, DOXAZOSIN, TERAZOSIN, PHENTOLAMINE, PHENOXY BENZAMINE**
- produce a competitive block of α1 -adrenoceptors.
- They decrease peripheral vascular resistance and lower arterial blood pressure by causing relaxation of both arterial and venous smooth muscle.
- Reflex tachycardia and postural hypotension often occur at the onset of treatment
- α-blockers are no longer recommended as initial treatment for hypertension, but may be used for refractory cases.

PHARMACOKINETICS:

- prazosin is always started at low dose (0.5 mg) given at bedtime
- gradually increased with twice daily
- administration till an adequate response is produced (max. dose 10 mg BD).
- An oral dose produces peak fall in BP after 4–5 hours and the effect lasts for nearly 12 hours,
- Plasma t½ is only 3 hours.

ADR:

- postural hypotension
- headache,
- drowsiness,
- dry mouth,
- weakness,
- palpitation,
- nasal blockade,
- blurred vision and rash.

β+α ADRENERGIC BLOCKERS:

– LABETALOL, CARNEDILOL

- They blocks α1, β1, and β2 receptors.
- Carvedilol, is mainly used in the treatment of heart failure.
- Carvedilol, as well as metoprolol succinate, and bisoprolol have been shown to reduce morbidity and mortality associated with heart failure.
- Labetalol is used in the management of gestational hypertension and hypertensive emergencies.

CENTRAL SYMPATHOLYTICS:

- Clonidine is a partial agonist with high affinity and high intrinsic activity at α2 receptors, especially α2A subtype in brainstem.
- stimulation of α2A receptors present mainly postjunctionally in medulla (vasomotor centre).
- This decreases sympathetic out flow → fall in BP and bradycardia.
- Enhanced vagal tone contributes to bradycardia.
- Clonidine is a moderately potent antihypertensive.

PHARMACOKINETICS:

- *Clonidine is well absorbed orally;*
- *Peak* occurs in 2–4 hours;
- 1/2 to 2/3 of an oral dose is excreted unchanged in urine, the rest as metabolites.
- Plasma t½ is 8–12 hours. Effect of a single dose lasts for 6–24 hours.

ADR:

- Sedation,
- mental depression,
- disturbed sleep;
- dryness of mouth, nose and eyes.

USE

- *popular antihypertensive* in the late 1960s and 1970s, but frequent side effects, risk of withdrawal hypertension and development of tolerance have relegated it to a 3rd or 4th choice drug.

Methyldopa

- This α-methyl analogue of dopa,
- The precursor of dopamine (DA) and NA is one of the first rationally designed antihypertensives.
- The α methyl-NA (a selective α2 agonist) formed in the brain from methyldopa acts on central α2 receptors
- decrease efferent sympathetic activity - decreases t.p.r. than HR or c.o.,
- α methyl NA is as potent vasoconstrictor as NA.
- Methyldopa is a moderate efficacy Antihypertensive.

ADR:

- ***lethargy and reduced mental*** **capacity**
- **Cognitive impairment**
- **Dryness of mouth,**
- **nasal stuffiness,**
- **headache,**
- **Fluid retention,**
- **weight gain,**
- **impotence**

Use :

- ***Methyldopa was a widely used antihypertensive,***
- **Used in combination with a diuretic.**

VASODILATORS

- Hydralazine/Dihydralazine
- Introduced in the 1950s,
- it is a directly acting arteriolar vasodilator with little action on venous capacitance vessels;
- reduces t.p.r. and causes greater decrease in diastolic than in systolic BP.
- They cause tachycardia, increase in c.o. and renin release → increased aldosterone → Na+ and water retention.
- The mechanism of vascular smooth muscle relaxant action of hydralazine is not clearly known.
- Interference with Ca2+ release, opening of certain
- K+ channels and/or NO generation may be involved.

ADR:

- Facial flushing,
- conjunctival injection,
- Throbbing headache,
- dizziness,
- palpitation,
- nasal stuffiness,

USE :

- *Hydralazine is now used as a second line* - alternative only in combination with a diuretic and/or β blocker for patients not achieving target BP with first line drugs.
- It is one of the preferred antihypertensives during pregnancy.
- Minoxidil - *Used in alopecia*

THANK YOU