Antihypertensive Drugs-I

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Hypertension:

- Hypertension is major risk factor for cardiovascular & renal diseases

1.Primary or essential hypertension:

- Definite cause for hypertension not known

2. Secondary hypertension:

- It is secondary to renal, endocrine or vascular causes

- **Renal causes for secondary hypertension:**
- Chronic diffuse glomerulonephritis
- Pyelonephritis
- Polycystic kidneys

- **Endocrine causes of secondary hypertension**
- Cushing syndrome
- Pheochromocytoma
- Primary hyperaldosteronism

- **Vascular causes:**
- Renal artery diseases
- Coarctation of aorta

Physiological control of BP:

- It is controlled by two major system:

i) Adrenergic nervous system

ii) The humoral renin-angiotensin- aldosterone system (RAAS)

Adrenergic Nervous system:

- This system acts through **baroreceptors**
- It will counteract acute changes in BP
- i.e. when one stands from lying down position, cardiac output falls due to reduced venous return→ fall in BP→ fainting
- This is normally prevented by baroreceptor reflex action→ ↑ HR & ↑ peripheral resistance

- The Humoral renin-angiotensin- aldosterone system (RAAS):

Kidney → Renin→ angiotensinogen

↓

Angiotensin I

↓ ----------ACE

Vasoconstriction ← Angiotensin II

↓

Angiotensin III

↓

Aldosterone

↓

Na+-Retention

↓

↑ Volume

- Renin is proteolytic enzyme produced & stored in kidney
- It is released in response to

a) Reduction in renal perfusion pressure

b) Reduction in sodium delivery to macula densa

c) Increase in sympathetic activity

d) Certain humoral factors

- Thus kidney plays important role in determination of blood pressure

Classification of Antihypertensive drugs:

- These drugs act by
- reducing the cardiac output and/or
- reducing total peripheral vascular resistance
- They are classified according to the site of action;

I. **Oral diuretics: Thiazides & Cholrthalidone**

II. RAAS inhibitors:

i) Blockers of renin release: Beta-adrenergic blockers

ii) Direct renin inhibitors: Aliskiren

iii) ACE inhibitors (ACEIs): Captopril, enalapril

iv) Angiotensin receptor blockers (ARBs): Losartan

v) Aldosterone antagonists: Spironolactone, eplerenone

III. Calcium channel blockers (CCBs):

Nifedipine,

amlodipine,

verapamil,

diltiazem

IV. Sympatholytic drugs:

i) Drugs acting on adrenergic receptors:

a) Alpha-adrenergic blocking agents: Phentolamine, phenoxybenzamine, prazosin, indoramin

b) Beta-adrenergic blocking agents: Propranolol, atenolol, metoprolol

c) Both alpha & beta adrenergic blocking agents: labetalol

ii) Central Sympatholytic drugs:

a) α2 adrenergic receptor stimulants: Clonidine, alpha-methyldopa

b) Selective imidazole receptor stimulants: Moxonidine

iii) Adrenergic neuron blockers : Guanethidine, reserpine

iv) Ganglion blocking agents : Hexamethonium, trimethaphan

v) Drugs acting directly on vascular smooth muscle (vasodilators):

a) Arteriolar vasodilators: Hydralazine, diazoxide, minoxidil

b) Arteriolar- venular vasodilators: Sodium nitroprusside

VI. Potassium channel activators: Diazoxide, minoxidil, pinacidil, nicorandil

VII. Miscellaneous: Metyrosine

Thiazides:

- They are useful in treatment of mild to moderate hypertension
- They enhance the effect of other antihypertensives

Mechanism of action:

- Initially, sodium depletion & reduction in plasma volume & cardiac output → ↓ BP

- Later, they act by decreasing systemic vascular resistance

- **Pharmacological actions:** Antihypertensive effect develops slowly
- They reduce both systolic as well as diastolic BP
- Very potent diuretic furosemide not recommended for long term management
- As it has short duration of action & serious electrolyte disturbance
- Maximum antihypertensive effect achieved at dose of 50 mg of thiazides & 12.5 – 25 mg of chlorthalidione

Adverse reactions:

- Hypokalemia
- Hyperuricaemia
- Hyperglycaemia
- But with recommended low doses these effects are not seen

Advantages of thiazides & chlorthalidione in low doses:

- They are useful in mild to moderate hypertension
- Postural hypotension is rare
- Blood flow to the vital organs like kidney & brain not compromised
- They do not cause reflex tachycardia or reduce cardiac output
- Unlike vasodilators they do not cause compensatory volume overload & oedema
- They are well tolerated & drug interactions are few
- They can be combined with other antihypertensive drugs with synergistic effects

RAAS Inhibitors:

Angiotensin-Converting Enzyme Inhibitors (ACEIs):

- Captopril was first ACEI introduced in 1981

Mechanism of action:

- ACEIs competitively inhibit ACE
- Thus it blocks the conversion of angiotensin I to angiotensin II
- Thus it prevents;
- a. The pressure effect of angiotensin II
- b. Stimulation of aldosterone synthesis & release
- c. The metabolism of bradykinin
- Levels of bradykinin are increased
- Bradykinin is potent vasodilator
- Thus it also contribute to antihypertensive & cardioprotective effects of ACEIs

Pharmacological actions:

- In hypertensive patients:
- ACEIs cause vasodilatation
- Thus it lowers systemic arterial resistance, lowers both SBP & DBP
- There is no reflex tachycardia
- Concurrent use of diuretics potentiate its effect
- Renal, cerebral & coronary blood flow is increased

- In patients with heart failure (HF): ACEI produce several beneficial effects;
- Afterload & preload is reduced.
- Cardiac output increases & heart rate decreased
- Following hemodynamic changes, natriuretic effect & reduction in aldosterone secretion
- Thus venous return to heart decreased→ ↓ preload

- Pulmonary arterial pressure, pulmonary capillary wedge pressure are reduced
- Left atrial & left ventricular filling pressure are reduced→ ↓ preload
- They reduce cardiac remodelling
- Exercise tolerance increased
- Survival is prolonged in Chronic HF
- In diabetic patients: ACEIs improve kidney function & reduce microalbuminurea
- Thus they are renoprotectives.

- In patients with acute MI, early administration within 24 hrs reduces LV dysfunction
- It also slows the progression of HF

Adverse reactions:

- These drugs are well tolerated
- Dry cough: due to inhibition of ACE due to raised levels of bradykinin
- A steep fall in BP after the first dose in patients with severe hypertension
- Hyperkalaemia due to aldosterone synthesis inhibition by ACEI

Doses:

- Captopril 12.5-50 mg BD
- Enalapril 5-20 mg OD
- Ramipril 2.5-20 mg OD

- **Therapeutic Uses:**
- Hypertension: They are useful in all grades of hypertension

- Combined with thiazide, they reduce thiazide induced hypokalaemia, hypercholesterolaemia, hyperglycaemia & hyperuricaemia

- They cab be used safely in asthma & diabetic patients

- There is no rebound hypertension on sudden stoppage

- They can be combined with antihypertensives of any other class

- They are well tolerated by elderly & do not affect sexual function

- ***Heart failure:***
- It is useful in all heart failure patients
- In patients with severe HF, reduce mortality & improve symptoms
- ***Diabetic nephropathy:***
- ACEIs are renoprotecive & decrease microalbuminurea
- ***Acute MI:*** They reduce LV dysfunction & mortality

- **Enalapril :**
- It is congener of Captopril
- Enalapril differs from Captopril
- It is a prodrug & converted to the active metabolite enalaprilat in liver
- Food does not interfere with absorption
- It is more potent
- It is less liable to cause taste disturbances, leucopenia & glomerulopathy

Contraindication for ACEI:

1. Severe bilateral renal artery stenosis

As they may reduce GFR & may cause renal failure

2. Aortic stenosis

3. Coarctation of the aorta

4. Pregnancy

Angiotensin Receptor Blockers (ARBs):

- ACEIs inhibit ACE
- ACE is not specific enzyme & has other substrates like bradykinin, substance P & neurokinins
- This may cause ADRs like cough & angioedema
- Hence specific ARBs have been developed.
- **Losartan:** It is phenyl tetrazole substituted imidazole compound
- It is selective competitive blocker of angiotensin I receptor type I (AT1)
- Thus it decreases the peripheral vascular resistance

- **ADRs:**
- As it is fetotoxic, contraindicated in pregnancy similar to ACEI
- It can precipitate renal failure in patients with bilateral renal artery stenosis
- Skin rashes, neuropsychiatric disturbances such as insomnia, confusion, nightmare, agitation & depression
- Analogues of Losartan: valsartan, Irbesartan, Eprosartan, Telmisartan, Candesartan, Olmesartan & Azilsartan

Aldosterone Antagonist:

Spironolactone:

- It is an add-on drug for hypertension
- It is indicated in patients with significant hyperuricaemia, hypokalaemia or glucose intolerance
- It is also indicated in resistant hypertension cases
- It is drug of choice in primary hyperaldosteronism
- Other aldosterone antagonist - eplerenone

Renin Inhibitors:

- These drugs inhibit renin
- Renin cleaves angiotensinogen from liver to form angiotensin I
- It is then converted to angiotensin II
- Thus it decreases both angiotensin I & Angiotensin II & reduces blood pressure.
- **Aliskiren:** This nonpeptide renin inhibitor

Calcium channel blockers(CCB):

- Calcium transport in myocardial & vascular smooth muscles involves:
- Voltage dependent channel - opens & closes in response to a voltage gradient
- There are two types of calcium channels in the heart L & T type.
- **Mechanism of action:** CCB binds to alpha-1 subunit of L-channel
- This inhibits entry of calcium into the myocardial & vascular smooth muscles
- Ultimately, decreasing the availability of intracellular calcium
- They are potent vasodilators

Classification of CCB:

- **I. Dihydropyridines (DHP):**
- i.e. Nifedipine & amlodipine
- **II. Non- dihydropyridines:**
- a. Phenylalkylamines: verapamil
- b. Benzothiazepines : Diltiazem
- **Pharmacological actions:**
- Antianginal action- improved coronary blood flow & decrease in oxygen demand of heart

- Effect on peripheral blood vessels:
- CCB relax vascular smooth muscles in systemic as well as pulmonary arterial circulations
- This lowers the vascular resistance & BP
- Thus useful in treatment of systemic & pulmonary hypertension
- Negative inotropic effects
- Antiarrythmic action

- **ADRs:**
- Headache, tachycardia, dizziness, fatigue, orthostatic hypotension, leg cramps, skin rashes & gingival hyperplasia
- Amlodipine & felodipine: They are second generation DHP CCBs
- They are potent coronary & peripheral vasodilators
- Other calcium channels blockers: verapamil, diltiazem, nifedipine, Nisoldipine & nimodipine

- Thus CCB are used in long term treatment of hypertension
- They are particularly used as monotherapy in patients with DM
- They are preferred drugs in patients with impaired renal function or asthma
- Diltiazem & amlodipine are effective in long term treatment of essential hypertension

Sympatholytic agents:

Adrenergic Receptor Blockers:

- These drugs will block either α or β or both adrenergic receptors

1. **α-adrenergic blocking agents:**

- Peripheral vascular α-receptors are of two types
- Post synaptic α1 receptors: these are stimulatory receptors causes vasoconstriction
- Presynaptic α2 receptors (autoreceptors): Inhibitory receptors
- Activation of these receptors causes inhibition of NA release

- Blockade of α1 receptor causes fall in BP
- While blocking of α2 receptors causes enhanced release of NA
- This released NA will act on cardiac β receptors & causes tachycardia
- Nonselective α blockers are not useful for essential hypertension as it causes palpitation & tachycardia

- **Phentolamine:** Nonselective α blocker
- It is used in **pheochromocytoma**
- It can also used to treat severe hypertension due to abrupt withdrawal of clonidine
- Dose: 2.5-10 mg
- **Phenoxybenzamine :** This is long acting competitive α blocker
- It is used in preoperative management of pheochromocytoma

- **Prazosin:** It is **selective α1 receptor blocker**
- It controls both supine & standing BP with minimal postural hypotension
- It dose not affect renal function, cardiac output or the RAAS
- It can be used in all grades of hypertension
- Selective α1 receptor blockers may decrease total, LDL cholesterol & triglycerides & increase HDL cholesterol level

- **ADRs:**
- Giddiness, drowsiness, tiredness, diarrhoea & fluid retention
- **First dose effect:** postural hypotension with first dose
- Dose : started with 1-3 mg/day in divided doses maintenance dose: 3-7.5 mg/day
- Other uses: benign prostatic hyperplasia, CHF
- Other analogues of prazosin: terazosin, doxazosin, alfuzocin, Indoramin

Central Sympatholytics:

- These drugs acts by stimulating the central α2 adrenergic receptors
- i.e. Clonidine

- **Mechanism of action:**

- 1) By activating adrenergic α2 receptors in vasomotor center & hypothalamus

- It causes decreased sympathetic outflow from CNS→↓ BP

2) They also act by stimulating peripheral inhibitory presynaptic α2 receptors – autoreceptors

- Thus, they reduce peripheral NA release

Pharmacological actions:

- They reduce both supine & standing BP without affecting cardiovascular reflexes
- Thus do not cause postural hypotension

- They do not affect renal blood flow & GFR
- Hence, they can be used in patients with renal insufficiency
- Reduce cardiac output, total peripheral resistance or both
- **ADRs:** Sedation, dry mouth, vertigo, constipation, parotid pain, impotence, GI disturbance
- Toxic doses causes bradycardia, miosis & hypotension
- Rebound rise in BP on abrupt cessation of clonidine therapy
- Preparation : Clonidine hydrochloride 0.1 mg tablet

- Therapeutic uses:
- Hypertension

- Menopausal hot flushes

- Opiate, alcohol, & nicotine withdrawal to control adrenergic symptoms

- **Alpha-methyldopa:**
- It is a prodrug

Mechanism of action:

- It is metabolized in adrenergic neuron to an active metabolite α methylnoradrenaline
- It is stored in vesicles of adrenergic neurons, instead of NA
- It is released on stimulation & acts on presynaptic α2 adrenergic receptors in brainstem
- Thus it inhibits central sympathetic outflow
- Pharmacological effects: Its hypotensive effect occurs after latent period of 3-6 h

- **Therapeutic uses:**
- Hypertension during pregnancy
- It is preferred drug due to its efficacy & safety in both mother & fetus.

Vasodilators:

- **Hydralazine:**
- It was tested for antihistaminic property, but later demonstrated its hypotensive action

- **Pharmacological actions:**
- Hydralazine lowers BP by direct relaxation of arteriolar wall

- Onset of action is slow

- Decrease in peripheral vascular resistance→↓BP → compensatory tachycardia → ↑cardiac output

Adverse Drug reactions:

- High incidence of ADR is main drawback of Hydralazine
- Gastrointestinal irritation
- Cardiac effects i.e. tachycardia, palpitation, anginal attacks
- **Preparation & doses:**
- Hydralazine hydrochloride tablets- 10, 25, 50 mg Maximum daily dose -100mg daily
- Injection 20 mg i.m. or i.v. use.

Sodium nitroprusside:

- It is given by i.v. infusion
- It is metabolized to its active compound Nitric oxide (NO)
- NO causes relaxation of arterioles & veins
- This result in reduction of peripheral vascular resistance & venous tone
- Thus, it lowers afterload & preload
- Myocardial oxygen consumption is reduced with improvement in myocardial function
- It is rapidly metabolized to thiocynate

Adverse reactions:

- Excessive accumulation of toxic cyanide – Hepatic dysfunction, metabolic acidosis, arrhythmia, hypotension & death
- Thiocynate toxicity: Fatigue, anorexia, nausea, vomiting, sweating, disorientation, psychotic behaviour & muscle twitching
- Preparation & dose: Sodium nitroprusside 50 mg powder to be dissolved in 5% dextrose just prior to administration

- **Therapeutic uses**:
- **Hypertensive emergencies**
- To produce controlled hypotension during surgery
- It is also used to improve left ventricular function in acute MI & low output states
- Dose: Slow i.v. infusion 0.5-5 mcg/kg/min

Potassium channel activators:

- Minoxidil & diazoxide used in hypertension
- Nicorandil & pinacidil used in angina
- **Mechanism of action:**
- Potassium channel play important role in regulation of membrane potential & excitability of cells
- Potassium channel activators combine with potassium channel → opening of these channels → potassium ions leak out from the cell → stabilization of cell membrane → reduces ca2+ entry leading to vasodilatation
- They play important role in management of IHD

Hypertension therapy:

- It is important to control BP – it will lead to end organ damage & subsequently mortality
- Aims of treatment of hypertension:
- Maintaining BP < 140/90 mm Hg without undue side effects
- Maintaining & improving the quality of life
- Reduction in left ventricular mass
- Prevention of cardiac arrhythmias, heart failure, stroke & other complications
- Control of other CHD risk factors

MCQs

Q 1. Which α adrenergic receptor blocking cause fall in BP

A) α1 receptors

B) α 2 receptors

C) Both α1 receptors & α 2 receptors

D) None of the above

Q 2. These are therapeutic uses of prazosin

A) benign prostatic hyperplasia

B) CHF

C) Hypertension

D) All of the above

Q 3. Pharmacological actions of β blockers are

A) Prevent tachycardia caused by vasodilators

B) They do not block baroreceptor mechanisms

C) Do not cause postural hypotension

D) All of the above

Q 4. This drug is preferred in hypertension during pregnancy

A) α methyldopa

B) Clonidine

C) Propranolol

D) Prazosin

Q 5. This is true about sodium nitroprusside

A) It is metabolized to its active compound Nitric oxide (NO)

B) It lowers afterload & preload

C) Myocardial oxygen consumption is reduced with improvement in myocardial function

D) All of the above

MCQs

Q 1. Which systems are involved for physiological control of BP;

A) Adrenergic system

B) RAAS

C) Both A & B are correct

D) None of the above

Q 2. Renin is released from the kidney in response to

A)Reduction in renal perfusion pressure

B) Reduction in sodium delivery to macula densa

C) Increase in sympathetic activity

D) All of the above

Q 3. Thiazide like diuretic exert their antihypertensive action by

A) Depletion of Na+ levels, decreasing plasma volume & cardiac output

B) Decreasing systemic vascular resistance

C) None of the above

D) A & B are correct

Q 4. This is true about ACEIs

A) It causes cough & angioedema

B) It is renoprotective

C) It can be safely used in asthma & diabetic patients

D) All of the above

Q 5. This is untrue about CCBs

A) They reduce coronary blood flow

B) They relax peripheral vascular smooth muscles

C) They can be used in hypertension with DM

D)They have Antiarrythmic action

Sr. No	Author	Topic	Journal /Book	Level
1	K D Tripathi	Antihypertensive drugs	Essentials of Medical Pharmacology, 8th edition	1
2	R S Satoskar	Pharmacotherapy of Hypertension, Pulmonary hypertension & Orthostatic hypotension	Pharmacology & Pharmacotherapeutics 25th Edition	1
3	Eduardo Hernandez-Vila, MD	A Review of the JNC 8 Blood Pressure Guideline	Texas Heart Institute Journal	3