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



- 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) $\alpha 2$ adrenergic receptor stimulants: Clonidine, alphamethyldopa
- 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

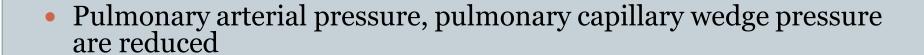
Mechanism of action:

- 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



- 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

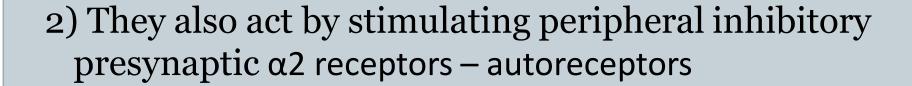
- Prazosin: It is selective α1 receptor blocker
- It controls both supine & standing BP with minimal postural hypotension
- It dose not affect renal function, cardiac output or the RAAS
- It can be used in all grades of hypertension
- Selective α1 receptor blockers may decrease total, LDL cholesterol & 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 $\alpha 2$ 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



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 $\alpha 2$ 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

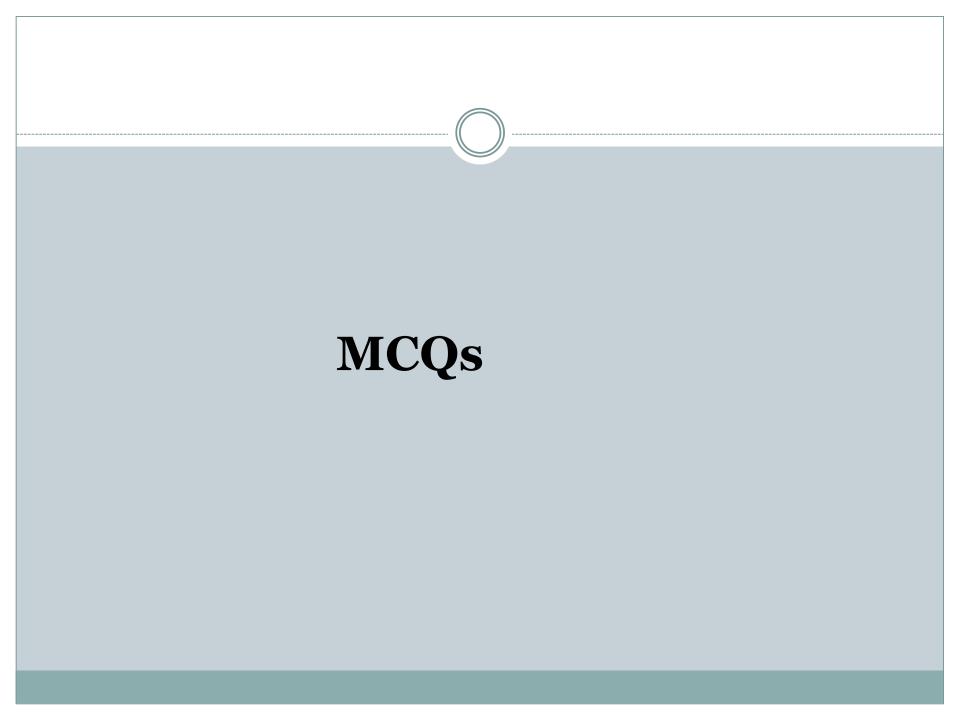
• Dose: Slow i.v. infusion 0.5-5 mcg/kg/min

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



$\bf Q$ 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

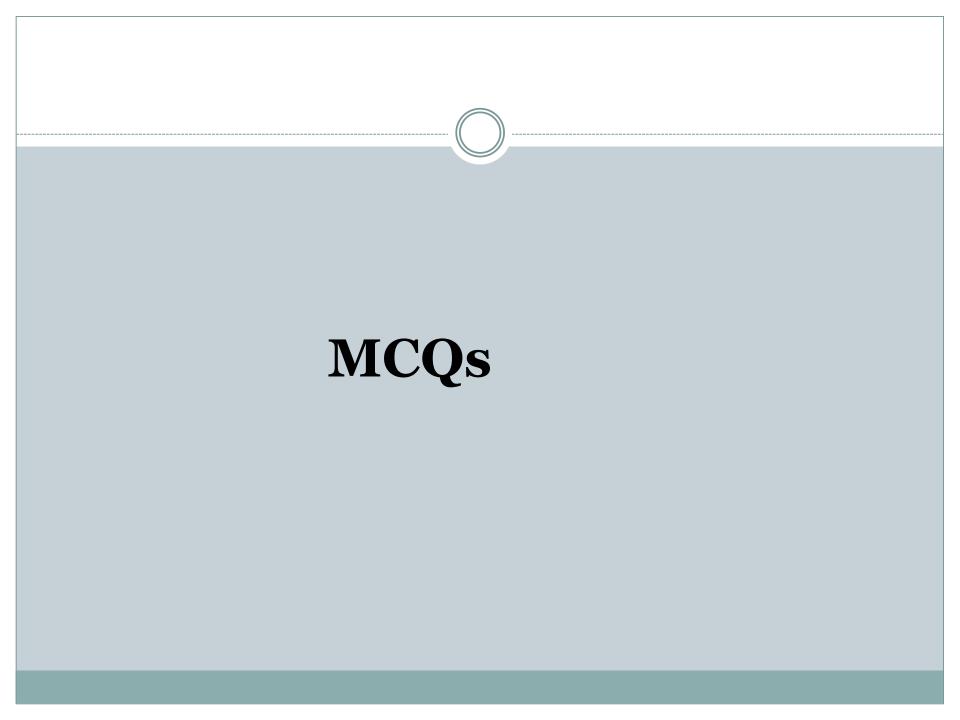
Q 4. This drug is preferred in hypertension during pregnancy

- 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



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 25 th Edition	1
3	Eduardo Hernandez- Vila, MD	A Review of the JNC 8 Blood Pressure Guideline	Texas Heart Institute Journal	3