

Antihypertensives

Overview

Hypertension is defined as either a sustained systolic blood pressure (SBP) of greater than 140 mm Hg or a sustained diastolic blood pressure (DBP) of greater than 90 mm Hg.

- Hypertension results from increased peripheral vascular smooth muscle tone, which leads to increased arteriolar resistance and reduced capacitance of the venous system.
- chronic hypertension either systolic or diastolic can lead to cerebrovascular accidents (strokes), congestive heart failure, myocardial infarction, and renal damage.

Mechanism for controlling B.P.

A- Baroreceptors and the sympathetic nervous system.

- A fall in blood pressure causes pressure-sensitive neurons (baroreceptors in the aortic arch and carotid sinuses) to send fewer impulses to cardiovascular centers in the spinal cord.
- This a reflex response of increased sympathetic and decreased parasympathetic output to the heart and vasculature, resulting in vasoconstriction and increased cardiac output.
- These changes result in a compensatory rise in blood pressure.

B- Renin-angiotensin-aldosterone system.

- Baroreceptors in the kidney respond to reduced arterial pressure (and to sympathetic stimulation of β -adrenoceptors) by releasing the enzyme renin.
- This enzyme converts angiotensinogen to angiotensin I, which is converted in turn to angiotensin II in the presence of angiotensin-converting enzyme (ACE). **1-** Angiotensin II is the body's most potent circulating vasoconstrictor, causing an increase in blood pressure. **2-** angiotensin II stimulates aldosterone secretion, leading to increased renal sodium reabsorption and increased blood volume.

The drugs used in the treatment of Hypertension:-

1- Diuretics

- Diuretics can be used as first-line drug therapy for hypertension unless there are compelling reasons to choose another agent.

- Low-dose diuretic therapy is safe, inexpensive, and effective in preventing stroke, myocardial infarction, and congestive heart failure, all of which can cause mortality.
- **Thiazide diuretics**:- Actions: **Thiazide** diuretics, such as **hydrochlorothiazide** lower blood pressure initially by increasing sodium and water excretion. This causes a decrease in extracellular volume, resulting in a decrease in cardiac output and renal blood flow.
- **Loop Diuretics** :- The loop diuretics act promptly, even in patients with poor renal function or who have not responded to thiazides or other diuretics. Loop diuretics cause decreased renal vascular resistance and increased renal blood flow.
- **Potassium-sparing diuretics**.
Amiloride and triamterene (inhibitors of epithelial sodium transport at the late distal and collecting ducts).

2- **β-Adrenoceptor Blocking Agents**:-

- The B-blockers reduce blood pressure primarily by **1-** decreasing cardiac output .They may also **2-** decrease sympathetic outflow from the central nervous system (CNS) **3-** inhibit the release of renin from the kidneys.
- The prototype B-blocker is **propranolol** which acts at both B1 and B2 receptors.
- Selective blockers of B1 receptors, such as **metoprolol** and **atenolol** are among the most commonly prescribed B- blockers.

Adverse effects

- Common effects: The **B**-blockers may cause bradycardia and CNS side effects such as fatigue, lethargy, insomnia, and hallucinations; these drugs can also cause hypotension.
- Drug withdrawal: Abrupt withdrawal may induce angina, myocardial infarction, or even sudden death in patients with ischemic heart disease. Therefore, the dose of these drugs must be tapered over 2 to 3 weeks in patients with hypertension and ischemic heart disease.

3- **ACE Inhibitors:Angiotensin converting enzyme inhibitors**.

- The ACE inhibitors, such as **enalapril** or **lisinopril**, are recommended when the preferred first-line agents (diuretics or B-blockers) are contraindicated or ineffective.

Actions:- The ACE inhibitors lower blood pressure by **1-** reducing peripheral vascular resistance, **2-** block the ACE that cleaves angiotensin I to form the potent vasoconstrictor angiotensin II.

4- Angiotensin II Receptor Antagonists:- The angiotensin II receptor blockers (ARBs) are alternatives to the ACE inhibitors. These drugs block the AT1 receptors. **Losartan** is the prototypic ARB; currently, there are six additional ARBs. **Candesartan , irbesartan, olmesartan, valsartan, telmisartan.**

5- Renin Inhibitors

- A selective renin inhibitor, **aliskiren** has been released for the treatment of hypertension.
- Aliskiren directly inhibits renin and, thus, acts earlier in the renin-angiotensin-aldosterone system than ACE inhibitors or ARBs.

6- Calcium-Channel Blockers: They are effective in treating hypertension in patients with angina or diabetes.

Classes of calcium-channel blockers:-

- **Verapamil** is the least selective of any calcium-channel blocker and has significant effects on both cardiac and vascular smooth muscle cells. It is used to treat angina, supraventricular tachyarrhythmias, and migraine headache.

B. Actions

- The intracellular concentration of calcium plays an important role in maintaining the tone of smooth muscle and in the contraction of the myocardium.
- Calcium-channel antagonists block the inward movement of calcium by binding to L-type calcium channels in the heart and in smooth muscle of the coronary and peripheral vasculature. This causes vascular smooth muscle to relax, dilating mainly arterioles.

7- α -Adrenoceptor Blocking Agents:- Prazosin, doxazosin and terazosin

- Produce a competitive block of α 1-adrenoceptors.
- They decrease peripheral vascular resistance and lower arterial blood pressure by causing relaxation of both arterial and venous smooth muscle.
- Prazosin is used to treat mild to moderate hypertension and is prescribed in combination with propranolol or a diuretic for additive effects.

8- Centrally Acting Adrenergic Drugs:-

a- Clonidine:-

- This α_2 -agonist diminishes central adrenergic outflow.
- **Clonidine** is used primarily for the treatment of hypertension that has not responded adequately to treatment with two or more drugs.

NOTE:- Rebound hypertension occurs following abrupt withdrawal of clonidine. The drug should therefore be withdrawn slowly if the clinician wishes to change agents.

b- α -methyldopa:-

This α_2 -agonist is converted to methylnorepinephrine centrally to diminish the adrenergic outflow from the CNS. This leads to reduced total peripheral resistance and a decreased blood pressure.

NOTE: It has been used in hypertensive pregnant patients.

9-Vasodilators

- The direct-acting smooth muscle relaxants, such as **hydralazine** and **minoxidil**. Vasodilators act by producing relaxation of vascular smooth muscle, which decreases resistance and, therefore, blood pressure.

a-Hydralazine

This drug causes direct vasodilation, acting primarily on arteries and arterioles. This results in a decreased peripheral resistance.

Hydralazine is used to treat moderately severe hypertension. **It is almost always administered in combination with β -blocker, such as propranolol (to balance the reflex tachycardia), and a diuretic (to decrease sodium retention).**

b- Minoxidil

This drug causes dilation of resistance vessels (arterioles) but not of capacitance vessels (venules). **Minoxidil** is administered orally for treatment of severe to malignant hypertension that is refractory to other drugs.

10-Hypertensive Emergency:-

a-Sodium nitroprusside:- Nitroprusside is administered intravenously and causes prompt vasodilation with reflex tachycardia. It is capable of reducing blood pressure in all patients regardless of the cause of hypertension

b-Labetalol:- Labetalol is both an α - and β -blocker and is given as an intravenous bolus or infusion in hypertensive emergencies.

c-Fenoldopam:- Fenoldopam is a peripheral dopamine-1 receptor agonist that is given as an intravenous infusion. fenoldopam maintains or increases renal perfusion while it lowers blood pressure. Fenoldopam can be safely used in all hypertensive emergencies and may be particularly beneficial in patients with renal insufficiency.

d-Nicardipine:- Nicardipine, a calcium-channel blocker, can be given as an intravenous infusion.



