Lecture -2- **د.رياض الموسوي**

Hypertension

5-. Diuretics

Diuretics can be used as first-line drug therapy for hypertension unless there are compelling reasons to choose another agent. Recent data suggest that diuretics are superior to β-blockers for treating hypertesnion in older adults.

A. Thiazide diuretics:- **hydrochlorothiazide**

All oral diuretic drugs are effective in the treatment of hypertension, but the thiazides have found the most widespread use.

M.O.A:-: Thiazide diuretics 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. With long-term treatment, plasma volume approaches a normal value, but peripheral resistance decreases.

Indications:-

Thiazide diuretics decrease blood pressure in both the supine and standing positions, and postural hypotension is rarely observed.

These agents counteract the sodium and water retention observed with other agents used in the treatment of hypertension (for example, hydralazine). Thiazides are therefore useful in combination therapy with a variety of other antihypertensive agents, including β-blockers, ACE inhibitors, angiotensin-receptor blockers, and potassium-sparing diuretics.

They are not effective in patients with inadequate renal function (creatinine clearance, <50 mL/min). Loop diuretics may be required in these patients.

S.E:-

1- hypokalemia and hyperuricemia in 70 percent of patients

2- hyperglycemia in 10 percent of patients.

3-Hypomagnesemia may also occur. Serum potassium levels should be monitored closely in patients who are predisposed to cardiac arrhythmias (particularly individuals with left

ventricular hypertrophy, ischemic heart disease, or chronic heart failure) and who are concurrently being treated with both thiazide diuretics and digoxin.

B-Loop diuretics:- **furosemode, bumetanide, ethacrynic acid, torsemide**

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. Loop diuretics increase the Ca2+ content of urine, whereas thiazide diuretics decrease it.

M.O.A:- Loop diuretics act on the ascending limb of the loop of Henle to inhibit sodium and chloride reabsorption.

Indications:-

1-Hypertension.

2-Oedema associated with heart failure, liver cirrhosis, renal impairment, nephrotic syndrome

S.E:-

hyponatremia, hypokalemia, hypomagnesemia, dehydration, hyperuricemia, gout, dizziness, postural hypotension, syncope.,dyslipidemia, increased serum creatinine, hypocalcemia,

C-Potassium-sparing diuretics. **Amiloride and triamterene**

Inhibitors of epithelial sodium transport at the late distal and collecting ducts as well as **spironolactone** and **eplerenone** (aldosterone-receptor antagonists) reduce potassium loss in the urine. **Spironolactone** has the additional benefit of diminishing the cardiac remodeling that occurs in heart failure.

6- Calcium-Channel Blockers

Calcium-channel blockers are recommended when the preferred first-line agents are contraindicated or ineffective.

-Classes of calcium-channel blockers

1-Dihydropyridines: This rapidly expanding class of calcium-channel blockers includes the first-generation ***nifedipine,*** 2nd generation ***amlodipine , felodipine , isradipine, nicardipine,*** **and** ***nisoldipine*****.** All dihydropyridines have a much greater affinity for vascular calcium channels than for calcium channels in the heart. They are therefore particularly attractive in treating hypertension. Some of the newer agents, such as ***amlodipine*** and ***nicardipine***, have the advantage that they show little interaction with

other cardiovascular drugs, such as *digoxin* or *warfarin*, which are often used concomitantly with calcium-channel blockers.

2-Diphenylalkylamines: *Verapamil* is the only member of this class that is currently approved. *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.

3-Benzothiazepines: *Diltiazem* is the only member of this class that is currently approved. Like *verapamil*, *diltiazem* affects both cardiac and vascular smooth muscle cells; however, it has a less pronounced negative inotropic effect on the heart compared to that of *verapamil*. *Diltiazem* has a favorable side-effect profile.

M.O.A:-

The intracellular concentration of calcium plays an important role in maintaining the tone of smooth muscle and in the contraction of the myocardium. Calcium enters muscle cells through special voltage-sensitive calcium channels. This triggers release of calcium from the sarcoplasmic reticulum and mitochondria, which further increases the cytosolic level of calcium. 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.

Indications:-

1-hypertensive patients who also have asthma, diabetes, angina, and/or peripheral vascular disease .

Pharmacokinetics

Most of these agents have short half-lives (3-8 hours) following an oral dose. Treatment is required three times a day to maintain good control of hypertension. Sustained-release preparations are available and permit less frequent dosing. ***Amlodipine*** has a very long half-life and does not require a sustained-release formulation.

S.E:-

Constipation occurs in 10 percent of patients treated with ***verapamil*.** Dizziness, headache, and a feeling of fatigue caused by a decrease in blood pressure are more

frequent with **dihydropyridines.** ***Verapamil*** should be avoided in patients with congestive heart failure or with atrioventricular block due to its negative inotropic effect.

7- Centrally acting adrenergic drugs:-

Clonidine

This α2-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. *Clonidine* does not decrease renal blood flow or glomerular filtration and, therefore, is useful in the treatment of hypertension complicated by renal disease. *Clonidine* is absorbed well after oral administration and is excreted by the kidney. Because it may cause sodium and water retention, *clonidine* may be administered in combination with a diuretic. Adverse effects are generally mild, but the drug can produce sedation and drying of the nasal mucosa. Rebound hypertension occurs following abrupt withdrawal of *clonidine*. The drug should therefore be withdrawn slowly if the clinician wishes to change agents.

α-Methyldopa

This α2-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. Cardiac output is not decreased, and blood flow to vital organs is not diminished. Because blood flow to the kidney is not diminished by its use, α-*methyldopa* is especially valuable in treating hypertensive patients with renal insufficiency. The most common side effects of Î±-*methyldopa* are sedation and drowsiness. It has been used in hypertensive pregnant patients.

8- Vasodilators:-

Hydralazine

This drug causes direct vasodilation, acting primarily on arteries and arterioles. This results in a decreased peripheral resistance, which in turn prompts a reflex elevation in heart rate and cardiac output. *Hydralazine* is used to treat moderately severe hypertension. It is almost always administered in combination with a β-blocker, such as *propranolol* (to balance the reflex tachycardia), and a diuretic (to decrease sodium retention). Together, the three drugs decrease cardiac output, plasma volume, and

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peripheral vascular resistance. *Hydralazine* monotherapy is an accepted method of controlling blood pressure in pregnancy-induced hypertension. Adverse effects of *hydralazine* therapy include headache, tachycardia, nausea, sweating, arrhythmia, and precipitation of angina. A lupus-like syndrome can occur with high dosage, but it is reversible on discontinuation of the drug.

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. Reflex tachycardia and fluid retention may be severe and require the concomitant use of a loop diuretic and a β-blocker. *Minoxidil* causes serious sodium and water retention, leading to volume overload, edema, and congestive heart failure. *Minoxidil* treatment also causes hypertrichosis (the growth of body hair). This drug is now used topically to treat male pattern baldness.]

Drugs used in emergency hypertension:-

1- Labetalol

2- Hydralazine

3- Fenoldopam

4- Nicardipine

5-

Na-nitroprusside.