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.

A. Thiazide diuretic:-

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

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. With long-term treatment, plasma volume approaches a normal value, but peripheral resistance decreases. Potassium-sparing diuretics are often used combined with thiazides.

Therapeutic uses:

Thiazide diuretics decrease blood pressure in both the supine and standing positions, and postural hypotension is rarely observed except in elderly, volume-depleted patients. 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. Thiazide diuretics are particularly useful in the treatment of black or elderly patients. They are not effective in patients with inadequate renal function (creatinine clearance, <50 mL/min). Loop diuretics may be required in these patients.

Pharmacokinetics:

Thiazide diuretics are orally active. Absorption and elimination rates vary considerably, although no clear advantage is present for one agent over another. All thiazides are ligands for the organic acid secretory system of the nephron, and as such, they may compete with uric acid for elimination.

Adverse effects:

Thiazide diuretics induce hypokalemia and hyperuricemia in 70 percent of patients and hyperglycemia in 10 percent of patients. 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:-

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.]

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.

Drugs Acting on CNS :-

A. 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.

C. 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 α-*methyldopa* are sedation and drowsiness. It has been used in hypertensive pregnant patients.

Hypertensive Emergency

Hypertensive emergency is a rare but life-threatening situation in which the DBP is either >150 mm Hg (with SBP>210 mm Hg) in an otherwise healthy person or >130 mm Hg in an individual with preexisting complications, such as encephalopathy, cerebral hemorrhage, left ventricular failure, or aortic stenosis. The therapeutic goal is to rapidly reduce blood pressure.

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. The drug has little effect outside the vascular system, acting equally on arterial and venous smooth muscle. [Because *nitroprusside* also acts on the veins, it can reduce cardiac preload.] *Nitroprusside* is metabolized rapidly (half-life of minutes) and requires continuous infusion to maintain its hypotensive action. *Sodium nitroprusside* exerts few adverse effects except for those of hypotension caused by overdose. *Nitroprusside* metabolism results in cyanide ion production. Although cyanide toxicity is rare, it can be effectively treated with an infusion of *sodium thiosulfate* to produce thiocyanate, which is less toxic and is eliminated by the kidneys. [Note: *Nitroprusside* is poisonous if given orally because of its hydrolysis to cyanide.] Nitroprusside is light sensitive, and when in solution, it should be protected from light.

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B. Labetalol

Labetalol is both an α- and a ß-blocker and is given as an intravenous bolus or infusion in hypertensive emergencies. *Labetalol* does not cause reflex tachycardia. *Labetalol* carries the contraindications of a nonselective ß-blocker. The major limitation is a longer half-life, which precludes.

C. Fenoldopam

Fenoldopam is a peripheral dopamine-1 receptor agonist that is given as an intravenous infusion. Unlike other parenteral antihypertensive agents, *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. The drug is contraindicated in patients with glaucoma.

D. Nicardipine

Nicardipine, a calcium-channel blocker, can be given as an intravenous infusion. The initial dose is 5 mg/h and can be increased to a maximum of 15 mg/h. The major limitation of *nicardipine* in treating hypertensive emergency is its long half-time (approximately 8 hours).

Hypertension In pregnancy :-

1- α-methyldopa I preeclapsia
2- Hydralazine in toxemia of pregnancy (eclampsia)
3- B-blockers may be used, but may causes fetal distress
4- ACEIs + Diuretics should be avoided

British guideline for management of hypertension :-

Step 1 :- ACEI or ARB or ß-blocker.
Step 2 :- one of the above drugs + CCB or Thiazides

Step 3 :- One of step 1 drugs + CCB + Thiazides
Step 4 (resistant hypertension) :- Add α-blocker or spiranolactone or other diuretics.