**Antihypertensive Drugs**

**I) Drugs That Alter Sodium & Water Balance (Diuretics).**

**a) Indapamide :** has direct vasodilator action.

**b) Thiazide diuretics :** are effective for mild-to-moderate hypertension in patients with normal renal and cardiac function.

**c) Potassium-sparing diuretics:** are useful to avoid excessive potassium depletion.

**d) Loop diuretics** are necessary in severe hypertension with: Multiple drugs that retain Na+ and water,

When GFR is < 30-40 mL/min,Cardiac failure,Cirrhosis when sodium retention is marked.

**II) Drugs That Alter Sympathetic Nervous System Function (Sympathoplegic agents).**

- All of these agents can elicit compensatory effects through adrenergic nerve-independent mechanisms: Retention of sodium by the kidney expansion of blood volume.

Thus, they are most effective when used concomitantly with a diuretic.

**1) Centrally acting sympathoplegic drugs.**

-less likely to produce postural hypotension.

**a) Methyldopa**

- stimulates central α2-adrenoceptors that mediate the negative feedback on catecholamine release.

- Used primarily for hypertension of pregnancy.

- Adverse Effects: Little postural hypotension, but may occur in volume-depleted patients, Lactation **, Positive Coomb’s test** in 10-20% of patients taking the drug for > 12 months: Makes cross-matching of blood difficult.

**b) Clonidine**

- direct agonist at central α2- adrenoceptors, decreases circulating catecholamine levels, and reduces blood pressure.

- After intravenous injection, it produces a brief rise in blood pressure followed by more prolonged hypotension.

- The pressor response is due to direct stimulation of α-adrenoceptors in arterioles.

- It reduces sympathetic and increases parasympathetic tone, resulting in blood pressure lowering and bradycardia.

- **clonidine** lowers heart rate and cardiac output more than does **methyldopa.**

- Reduction in arterial blood pressure by clonidine and methyldopa is accompanied by decreased renal vascular resistance and maintenance of renal blood flow.

**- Adverse effects**: Dry mouth and sedation , should not be given to **patients who are at risk for mental depression** , **Concomitant treatment with tricyclic antidepressants** may block the antihypertensive effect of clonidine due to α-adrenoceptor-blocking actions of the tricyclics , **Withdrawal of clonidine** after prolonged use can result in life-threatening hypertensive crisis , **withdrawal syndrome** .

- **Treatment of the hypertensive crisis** consists of reinstitution of clonidine therapy or administration of both α- and β-adrenoceptor-blocking agents.

**2) Ganglion-blocking agents.**

**3) Adrenergic neuron-blocking agents.**

**4) Adrenoceptor antagonists.**

**a) β-Adrenoceptor Antagonists**

- **Propranolol** (non-selective, blocks β1- and β2-adrenoceptors) has been replaced by cardioselective β1-blockers such as **bisoprolol, metoprolol and atenolol.**

- In severe hypertension, they are especially useful in preventing the reflex tachycardia that results from treatment with direct vasodilators

- They reduce mortality after a myocardial infarction, and some also reduce mortality in patients with heart failure.

- Reduce blood pressure without prominent postural hypotension.

- **adverse effects :** Major adverse effects: Bradycardia (β1-block) , Cardiac block (β1-block) ,Increased peripheral vascular resistance (β2-block) ,Bronchoconstriction (β2-block) ,Masking signs and symptoms of hyperglycemia, Withdrawal syndrome.

**b)α-Adrenoceptor Antagonists**

- **Prazosin, terazosin**, and **doxazosin** are selective α1-receptors blockers in arterioles and venules dilation.

- **Phentolamine** (nonselective α antagonists) blocks both presynaptic and postsynaptic α- receptors which results in reflex activation of sympathetic neurons and greater release of norepinephrine and greater cardio-acceleration.

- Retention of salt and water is a recognized **adverse effect.**

- The drugs are more effective when used in combination with other agents, such as a β blocker and a diuretic, than when used alone.

- **used primarily in men with concurrent hypertension and benign prostatic hyperplasia and bladder neck obstruction.**

**III) Direct vasodilators**

- Inadequate as monotherapy for hypertension because of tolerance, but more useful when combined with diuretics and/or β-blockers.

1) **Hydralazine**

- acts mainly by releasing **nitric oxide (NO), EDRF.** - It dilates arterioles but not veins

- There is genetic defects in the capacity to acetylate the drug.

**- Adverse effects**: Headache, flushing, nasal congestion, palpitations, tachycardia, and thus, myocardial ischemia, **Zupus-erythematosus like syndrome** especially in slow acetylators (arthralgia, myalgia, skin rashes, and fever, but no renal damage).

2) **Minoxidil**

- **It dilates arterioles but not veins.**

**- Adverse effects**: Headache, flushing, nasal congestion, palpitations, tachycardia, and thus, myocardial ischemia , **Growth of body hair (hypertrichosis).**

- Can be used for male pattern baldness topically (**Rogaine**), but the effect is lost after stopping the drug.

3) **Diazoxide**

- Chemically similar to thiazide diuretics but without a diuretic action

- **Therapeutic uses:** Hypertensive emergency , Insulinomas .

**-Adverse effects**: hypotension , hyperglycemia , may stop labor if used in pregnancy

4) **Sodium Nitroprusside**

- It dilates both arterial and venous vessels, resulting in reduced peripheral vascular resistance and venous return.

- **Used for hypertensive emergencies, and severe heart failure.**

- Has a short duration of action after IV injection (~ 2 min), and should be infused continuously but not more than one hour. The effect dissappears after 1-10 min of discontinuation.

**- Adverse effects**: Postural hypotension , Methemoglobinemia , Accumulation of cyanide , Prolonged treatment may produce **thiocyanate toxicity** especially in patients with renal failure.

- **sodium thiosulfate** and **nontoxic cyanocobalamin** can be used for prophylaxis or treatment of cyanide poisoning during nitroprusside infusion.

5) **Fenoldopam**

- an arteriolar dilator

- Used for hypertensive emergencies and postoperative hypertension.

- **Adverse effects:** reflex tachycardia, headache, flushing, and increased intraocular pressure.

6) **Calcium Channel Blockers**

- their metabolism is inhibited by grapefruit juice.

- **Verapamil and diltiazem** bind to related but not identical receptors.

- Improve angina of effort by reduction of peripheral vascular resistance, and relieve of coronary artery improves variant angina.

- **(Verapamil, Diltiazem)** can cause congestive heart failure.

- **Verapamil and diltiazem** should NOT be co- administered with β-blockers.

- **Dihydropyridines** can be combined with **verapamil and diltiazem.**

**a) Verapamil**

- inhibits Potassium channels in vascular smooth muscle.

- Blockade of vascular smooth muscle potassium channels reduce the effect of verapamil on vasodilation.

- **Verapamil** blocks p-glycoproteins, efflux-transporter, and thus, may reduce resistance of cancer cell to chemotherapeutic agents.

**b) Diltiazem**

- Women may be more sensitive than men to the hypotensive action of diltiazem.

**c) Dihydropyridines: Nifedipine, Amlodipine, Nicardipine**

- bind to one type of receptors.

- are more selective to vascular smooth muscle ↔ negligible effect on cardiac myocytes.

- may differ in potency in different vascular beds.

- Dihydropyridines are not effective on cardiac muscle.

- casue reflex tachycardia , renin secretion: retention of Na+ and water & vasoconstriction.

- Immediate release short-acting dihydropyridines can precipitate angina pectoris in patients with coronary artery disease

**\* Therapeutic Uses: Hypertension , angina pectoris and myocardial infarction , Supraventricular tachyarrhythmia's (NOT the dihydropyridines).**

**\* Adverse Effects:** Cardiac depression , Flushing, dizziness, nausea, constipation and peripheral edema

**IV) Inhibitors of the Renin- Angiotensin-Aldosterone System**

**\*Classification:**

**1) β-Adrenoceptor blockers.**

**2) Renin antagonist: aliskiren**

**3) Angiotensin converting enzyme inhibitors (ACEI’s)**

- Inhibit peptidyl dipeptidase that hydrolyzes angiotensin I to angiotensin II which inactivates bradykinin (plasma kininase), a potent vasodilator.

- They do NOT cause reflex sympathetic stimulation .

**Captopril –** short acting.

**Enalapril –** prodrug (enalaprilat, IV).

**Lisinopril –** derivative of enalaprilat.

**Ramipril, benazepril, fosinopril, moexipril, perindopril, quinapril, and trandolapril: prodrugs – long acting**

**- They are effective in hypertensive patients irrespective of plasma renin activity.**

**\* Clinical Pharmacology:** hypertension , diabetic nephropathy (even without hypertension) , Heart failure , Myocardial infarction , Reduce the incidence of diabetes in patients with high cardiovascular risk.

**\* Adverse Effects:**

**1)** Severe hypotension after initial doses especially in hypovolemia as a result of diuretics, salt restriction, or gastrointestinal fluid loss.

2) Acute renal failure , Hyperkalemia , Dry cough, wheezing, angioedema .

3) **Captopril** may cause proteinuria and neutropenia at high doses, especially in patients with renal insufficiency.

4) **Contraindicated during pregnancy**: Fetal hypotension, anuria, renal failure, malformations and death.

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**4) Angiotensin receptor blockers.**

**- Losartan, Valsartan, Candesartan, eprosartan, irbesartan, telmisartan, and olmesartan.**

**-** Block angiotensin II type 1 receptors (AT1-R).

- Adverse effects are similar to ACEIs except, wheezing, angioedema and cough which may occur much less commonly.

**5) Aldosterone antagonists – spironolactone**

\***Treatment of Angina Pectoris:**

- **In effort angina**, oxygen demand can be reduced by decreasing cardiac work.

- **In variant angina**, spasm of coronary vessels can be reversed by nitrate or calcium channel-blocking vasodilators.

- **In unstable angina**, vigorous measures are taken to achieve both increased oxygen delivery, and decreased oxygen demand.

- **Lipid-lowering drugs, especially the “statins,”** have become extremely important in the long-term treatment of atherosclerotic disease.

**1)** **Reduction of overall myocardial O2 demand:**

**Organic nitrates**

**Calcium channel blockers**

**β- Adrenoceptor blockers**

**2) Increase of blood flow, and thus, O2 supply, in the coronaries:**

**Organic nitrates**

**Calcium channel blockers**

**β-adrenoceptor But not blockers (not vasodilators)**

**\* Drugs used in the treatment of Angina Pectoris:**

**1) Nitrates & Nitrites**

**A. Moderately volatile liquids: Nitroglycerin**

**B. Solids: Isosorbide dinitrate, Isosorbide mononitrate**

**\*Isosorbide 5-mononitrate** has a bioavailability of 100%.

**\* Therapeutic Uses:** Typical angina , Prinzmetal’s angina , Unstable angina , Myocardial infarction,

 Congestive heart failure, Hypertension.

**\* Adverse Effects:** Orthostatic hypotension ,Throbbing headache due to temporal and meningeal artery pulsations, Reflex sympathetic discharge ,tachycardia ,Sodium and water retention Increased intracranial pressure ,Tolerance.

**2) Nicorandil**

- dilates normal coronary arteries, by activating potassium channels.

**3) Molsidomine**

- prodrug that is converted to a nitric oxide-releasing metabolite.

- have efficacy comparable to that of the organic nitrates without development of tolerance.

**4) Ranolazine**

- reduces intracellular calcium concentration .

- It is effective in stable angina, but it does not reduce the incidence of death in acute coronary syndromes.

- It may inhibit the metabolism of digoxin and simvastatin.

**5) Trimetazidine**

- pFOX inhibitors (**trimetazidine**) partially inhibit the fatty acid oxidation pathway in myocardium.

- It is effective in stable angina.

**6) Fasudil**

- inhibitor of smooth muscle Rho kinase and reduces coronary vasospasm and has improved

performance in stress tests.

**7) β-Adrenoceptor Blockers**

- Decrease mortality in patients with recent MI - Reduce infarct size - Not useful in variant angina.

**8) Ca+2 channel Blockers**

- Useful in variant angina

**9) Ivabradine**

- Bradycardic drug.

- relatively selective If sodium channel blockers

- Reduces cardiac rate by inhibiting the hyperpolarization-activated sodium channel in the sinoatrial node.

- Used in angina and heart failure.

**10) Statins**

- They are indicated after myocardial infarction irrespective of cholesterol level in the plasma.

- Started immediately after MI with antiplatelets and ACEIs.

- Reduce myocardial events and reduce mortality after MI.