Pharmacotherapy of Hypertension (HTN)

Definition

- A sustained increase in blood pressure (≥130/80 mm Hg) [on repeated BP measurement]
- Criteria for HTN in Adults

Classification	Blood Pressure (mm Hg)		
	Systolic		Diastolic
Normal	< 120	&	< 80
Elevated	120 – 129	/	< 80
Hypertension, Stage 1	130 – 139	/	80 – 89
Hypertension, Stage 2	≥ 140	/	≥ 90

- Sustained arterial hypertension damages blood vessels in **kidney**, **heart** and **brain** and leads to an increased incidence of **renal failure**, **cardiac failure**, and **stroke**.
- Effective pharmacologic lowering of blood pressure prevents the damage to blood vessels and reduces the morbidity and mortality rate.

- Two factors which determine blood pressure are **cardiac out put** (stroke volume x heart rate) and **total peripheral resistance** of the vasculature.
- Blood pressure is regulated by an interaction between nervous, endocrine and renal systems
- Elevated blood pressure is usually caused by a combination of several abnormalities such as psychological stress, genetic inheritance, environmental and dietary factors and others.
- Patients in whom no specific cause of hypertension can be found are said to have essential hypertension or primary hypertension (accounts for more than 90 % of cases).
- Secondary hypertension arises as a consequence of some other conditions such as, atherosclerosis, renal disease, endocrine diseases and others.
- The central issue of antihypertensive therapy is to lower arterial blood pressure, irrespective of the cause.
- The choice of therapy of a patient with hypertension depends on a variety of factors: age, sex, race, body build, life-style of the patient, cause of the disease, other co-existing disease, rapidity of onset and severity of hypertension, and the presence or absence of other risk factors for cardiovascular disease (e.g. smoking, alcohol consumption, obesity, and personality type).

Antihypertensive therapies.

Non pharmacological therapy of hypertension

- Several non-pharmacological approaches to therapy of hypertension are available.
  - ✓ Low sodium chloride diet
  - ✓ Weight reduction
  - ✓ Exercise
  - ✓ Cessation of smoking
  - ✓ Decrease in excessive consumption of alcohol
  - ✓ Psychological methods (relaxation, meditation …etc)
  - ✓ Dietary decrease in saturated fats.
- On the average, only modest reductions (5 to 10 mmHg) in blood pressure can be achieved.
- This may be sufficient for the treatment of some mild hypertensive cases.
- The major advantage of non-pharmacological approaches is the relative safety and freedom from side effects, compared with drug therapy.

Pharmacological therapy of hypertension.

- Currently available drugs lower blood pressure by decreasing either cardiac output (CO) or total peripheral vascular resistance (PVR) or both
- A) **Diuretics**, which lower blood pressure by depleting the body sodium and reducing blood volume.
- Diuretics are effective in lowering blood pressure by 10 – 15 mmHg in most patients.

B) Sympathoplegic agents (Depressants of sympathetic activity).

- sympathoplegic drugs are divided into:
  a) **Centrally acting antihypertensive agents** e.g. methyldopa, clonidine
- Centrally acting sympathetic depressants act by stimulating α_2-receptors located in the vasomotor centre of the medulla.
- As a result, sympathetic out flow from the medulla is diminished and either total peripheral resistance or cardiac out put decreases.
- Methyldopa is useful in the treatment mild to moderately severe hypertension.
- Methyldopa is a prodrug and must be converted in the CNS to active α – methylnorepinephrine to exert the effect on blood pressure.
- The side effects of methyldopa include sedation, vertigo, dry mouth, nausea, vomiting, diarrhea, postural hypotension, impotence, haemolytic anemia, weight gain and hypersensitivety reactions (fever, liver damage, thrombocytopenia).

b) Adrenoceptor antagonists, e.g propranolol (beta blocker), prazosin (alpha blocker), labetalol (alpha and beta blocker).

- β – Blockers antagonize beta, receptors located on the myocardium and prevent the cardio acceleration, which follows sympathetic stimulation.
- The rate and force of myocardial contraction is diminished, decreasing cardiac out put and thus, lowering blood pressure.
- An additional effect which can contribute to a reduction of blood pressure is that renin release is mediated by β receptors.
- Therefore, receptor blockade prevents angiotensin II formation and associated aldosterone secretion, resulting in a decrease in total peripheral resistance and blood volume.
- The principal action of alpha adrenergic blocking drugs is to produce peripheral vasodilation.
- Alpha blockers reduce arterial pressure by dilating both resistance and capacitance vessels.
- Treatment with prazosin should be initiated with low dose (1mg 3 times daily) to prevent postural hypotension and syncope or be given at bed time.

c) Adrenergic neuron – blocking agents, e.g. guanethidine

- Guanethidine is an adrenergic neuron-blocking drug recommended for treatment of severe forms of hypertension.
- Guanethidine blocks adrenergic nerve transmission, preventing the release of transmitter.
- It lowers blood pressure by reducing both cardiac out put and total peripheral resistance.

d) Drugs which deplete catecholamine stores, e.g. reserpine.

- ❖ Reserpine interferes with the storage of endogenous catecholamines in storage vesicles as a result of which little neurotransmitter is released upon stimulation.
- ❖ It leads to reduction of cardiac out put and peripheral vascular resistance.
- ❖ Reserpine is a second-line drug for treatment of hypertension.

e) Ganglion blockers, e.g. trimethaphan

- ❖ Trimethaphan is ganglion blocking drug which is reserved for use in hypertensive emergencies only.

C) Direct vasodilators. These include:-

- ✓ Arterial vasodilators, e.g. hydralazine
- ✓ Arteriovenous vasodilators, e.g. sodium nitroprusside

❖ ***Hydralazine:*** It dilates arterioles but not veins.

- It is used particularly in severe hypertension.
- The most common adverse effects are headache, nausea, anorexia, palpitations, sweating and flushing which are typical to vasodilators.

❖ ***Sodium nitroprusside:*** It is a powerful vasodilator that is used in treating hypertensive emergencies as well as severe cardiac failure.

- It dilates both arterial and venous vessels, resulting in reduced peripheral vascular resistance and venous return.
- Nitroprusside rapidly lowers blood pressure and it is given by intravenous infusion.
- The most serious toxicities include metabolic acidosis, arrhythmias, excessive hypotension and death.

❖ **D) Angiotensin converting enzyme inhibitors,** e.g. captopril, enalapril, etc.

- The prototype is captopril.
- Captopril inhibits angiotensin converting enzyme that hydrolyzes angiotensin I (Inactive) to angiotensin II (Active), a potent vasoconstrictor, which additionally stimulates the secretion of aldosterone.
- It lowers blood pressure principally by decreasing peripheral vascular resistance.
- The adverse effects include maculopapular rash, angioedema, cough, granulocytopenia and diminished taste sensation.
- Enalapril is a prodrug with effects similar to those of captopril.

E) Calcium channel blockers, e.g. nifedipine, verapamil, nicardipine, etc.

- The prototype is verapamil.
- The mechanism of action in hypertension is inhibition of calcium influx in to arterial smooth muscle cells, resulting in a decrease in peripheral resistance.
- Verapamil has the greatest cardiac depressant effect and may decrease heart rate and cardiac out put as well.
- The most important toxic effects for calcium channel blockers are cardiac arrest, bradycardia, atrioventricular block and congestive *heart failure.*

Lines of treatment of primary hypertension

- The initial step in treating hypertension may be non-pharmacologic.
- Dietary salt restriction may be effective treatment for about half of the patients with mild hypertension.
- Weight reduction even without salt restriction normalizes blood pressure in up to 70% of obese patients with mild to moderate hypertension.
- Regular exercise may also be helpful in some hypertensive patients.
- When non-pharmacologic approaches do not satisfactorily control blood pressure, drug therapy begins in addition to non-pharmacological approaches.
- The selection of drug(s) depends on various factors such as the severity of hypertension, patient factors (age, race, coexisting diseases, etc.).

- For most patients with mild hypertension and some patients with moderate hypertension monotherapy with either of the following drugs can be sufficient.
  - ✓ Thiazide diuretics
  - ✓ Beta blockers
  - ✓ Calcium channel blockers
  - ✓ Angiotensin converting enzyme inhibitors
  - ✓ Central sympathoplegic agents
- Beta-blockers are preferred in young patients, high renin hypertension and patients with tachycardia or angina and hypertension.
- Black patients respond well to diuretics and calcium channel blockers than to beta-blockers and ACE inhibitors.

- If mono-therapy is unsuccessful, combination of two drugs with different sites of action may be used.
  - ✓ Thiazide diuretics may be used in conjunction with a beta-blocker, calcium channel blocker or an angiotensin converting enzyme inhibitor.
- If hypertension is still not under control, a third drug e.g. vasodilator such as hydralazine may be combined.
- When three drugs are required, combining a diuretic, a sympathoplegic agents or an ACE inhibitor, and a direct vasodilator or calcium channel block is effective.
- The treatment of hypertensive emergencies is usually started with furosemide given by parenteral route at dose of 20-40mg.
- In addition, parenteral use of diazoxide, sodium nitroprusside, hydralazine, trimethaphan, labetalol can be indicated.

Drug used in heart failure

- Congestive heart failure occurs when there is an inability of the heart to maintain a cardiac out put sufficient to meet the requirements of the metabolising tissues.
- Heart failure is usually caused by one of the following:
  - ✓ Ischaemic heart disease,
  - ✓ Hypertension,
  - ✓ Heart muscle disorders, and
  - ✓ Valvular heart disease.
- Drugs used to treat heart failure can be broadly divided into:

  A. Drugs with positive inotropic effect.

  B. Drugs without positive inotropic effect.

A. Drugs with positive inotropic effect:-

- Drugs with positive inotropic effect increase the force of contraction of the heart muscle. These
- include:
  - ✓Cardiac glycosides,
  - ✓Bipyridine derivatives,
  - ✓Sympathomimetics, and
  - ✓Methylxanthines

Cardiac glycosides.

- Cardiac glycosides comprise a group of steroid compounds that can increase cardiac out put and alter the electrical functions.
- Commonly used cardiac glycosides are digoxin and digitoxin.
- The mechanism of inotropic action of cardiac glycosides is inhibition of the membrane-bound Na/K ATPase often called the "*Sodium Pump*".
- This results in an increased intracellular movement of sodium and accumulation of sodium in the cells.
- As a consequence of the higher intracellular sodium, decreased transmembrane exchange of sodium and calcium will take place leading to an increase in the intracellular calcium that acts on contractile proteins.
- All cardiac glycosides exhibit similar pharmacodynamic properties but do differ in their pharmacokinetic properties.
- For example, digitoxin is more lipid soluble and has long half-life than digoxin.

❖ **Therapeutic uses of cardiac glycosides include:**

- Congestive heart failure
- Atrial fibrillation,
- Atrial flutter, and
- Paroxysmal atrial tachycardia.

❖ **Toxicity of cardiac glycosides include:**

- Gastrointestinal effects such as anorexia, nausea, vomiting, diarrhoea Cardiac effects such as bradycardia, heart block, arrhythmias CNS effects such as headache, malaise, hallucinations, delirium, visual disturbances (yellow vision) Mild toxicities such as gastrointestinal and visual disturbance can be managed by reducing the dose of the drug.

- For the management of arrhythmias or serious toxicity, potassium supplementation, administration of anti-arrhythmic drugs (e.g. lidocaine), and use of digoxin antibodies can be helpful.

❖ ***Bipyridine derivatives, e.g. amrinone, milrinone.***

- These drugs possess both positive inotropic effect and vasodilator effects.
- The suggested mechanism of action is inhibition of an enzyme known as phophodiesterase, is responsible for the inactivation of cyclic AMP.
- Inhibition of this enzymes result in an increase in cAMP.
- Bipyridine derivatives are used in cases of heart failure resistant to treatment with cardiac glycosides and vasodilators.

- ***Beta - adrenergic stimulants*** e.g. dobutamine, dopamine
  - The increase in myocardial contractility by beta stimulants increase the cardiac out put.
  - However, positive chronotropic effect of these agents minimizes the benefit particularly in patients with ischaemic heart disease.
  - The positive inotropic effect of dobutamine is proportionally greater than its effect on heart rate.
  - It is reserved for management of acute failure or failure refractory to other oral agents.
- **Methylxanthines,** e.g. theophylline in the form of aminophylline
  - Aminophylline has a positive inotropic effect, bronchodilating effect and a modest effect on renal blood flow.
  - It is used for management of acute left ventricular failure or pulmonary edema.

B. Drugs without positive inotropic effect.

- These include:
  - ✓ Diuretics, e.g. hydrochlorothiazide, furosemide
  - ✓ Vasodilators, e.g. hydralazine, sodium nitroprusside
  - ✓ Angiotensin converting enzyme inhibitors e.g. captopril, enalapril

Diuretics

- Diuretics are first – line drugs for treatment of patients with heart failure. In mild failure, a
- thiazide may be sufficient but are ineffective at low glomerular filtration rates.
- Moderate or severe failure requires a loop diuretic.
- In acute failure, diuretics play important role by reducing ventricular preload.
- The reduction in venous pressure causes reduction of edema and its symptoms and reduction of cardiac size which leads to improved efficiency of pump function.

Vasodilators.

- Vasodilators are effective in acute heart failure because they provide a reduction in preload (through venous dilation), or reduction in after-load (through arteriolar dilation), or both.
- Hydralazine has a direct vasodilator effect confined to arterial bed.
- Reduction in systemic vascular resistance leads to a considerable rise in cardiac out put.
- Sodium nitroprusside is a mixed venous and arteriolar dilator used also for acute reduction of blood pressure.
- Vasodilator agents are generally reserved for patients who are intolerant of or who have contraindications to ACE inhibitors.

*Angiotensin c*onverting enzyme (ACE) inhibitors.

- Because of the pervasive involvement of angiotensin II in the undesirable compensatory responses to heart failure, reduction of this peptide has positive effects on the course of the disease.
- These drugs reduce after load by reducing peripheral resistance and also reduce preload by reducing salt and water retention by way of reduction in aldosterone secretion.
- They are nowadays considered a head of cardiac glycosides in the treatment of chronic heart failure.
- The following are essential for long-term management of chronic heart failure:

✓ Modify cardiovascular risk factor profile, e.g. cigarette smoking, obesity, salt intake Underlying

✓ causes should be treated, e.g. anemia, hypertension, valvular disease If this proves inadequate, diuretic should be given.

✓ Give ACE inhibitor and digitalis (ACE inhibitors may be used before digitalis). In patients with persisting symptoms give vasodilators besides increasing the dose of diuretic and ACE inhibitors.

Pharmacotherapy of Angina pectoris

- Angina pectoris develops as a result of an imbalance between the oxygen supply and the oxygen demand of the myocardium.
- It is a symptom of myocardial ischemia.
- When the increase in coronary blood flow is unable to match the increased oxygen demand, angina develops.
- It has become apparent that spasm of the coronary arteries is important in the production of angina.

Drugs used in angina pectoris

- **Organic nitrates** e.g. nitro-glycerine, isosorbide dinitrate, etc.
- **Beta adrenergic blocking agents** e.g. propranolol, atenolol, etc.
- **Calcium channel blocking agents** e.g. verapamil, nifedipine, etc.
- **Miscellaneous drugs** e.g. aspirin, heparin, dipyridamole.

❖ ***Organic nitrates:*** organic nitrates are potent vasodilators and successfully used in therapy of angina pectoris for over 100 years.

- The effects of nitrates are mediated through the direct relaxant action on smooth muscles.
- Nitrates are believed to act by mimicking the vasodilator action of endothelium derived relaxing factor (EDRF) identified as nitric oxide.
- Vasodilating organic nitrates are reduced to organic nitrites, which is then converted to nitric oxide.
- *The action of nitrates begins after 2-3* minutes when chewed or held under tongue and action lasts for 2 hours.
- The onset of action and duration of action differs for different nitrates and varying pharmaceutical preparations.

❖ ***Adverse effects*** *include* flushing, weakness, dizziness, tachycardia, palpitation, vertigo, sweating, syncope localized burning with sublingual preparation and contact dermatitis with ointment.

❖ ***Therapeutic uses***: prophylaxis and treatment of angina pectoris, post myocardial infarction, coronary insufficiency, acute LVF (left ventricle failure)

Adrenergic blocking agents

- Exercise and emotional excitement induce angina in susceptible subject by the increase in heart rate, blood pressure and myocardial contractility through increased sympathetic activity.
- Beta receptor blocking agents prevent angina by blocking all these effects.
- In most patients the net effect is a beneficial reduction in cardiac workload and myocardial oxygen consumption e.g. atenolol, propranolol metoprolol, labetolol.
- ***Adverse effects:*** Lethargy, fatigue, rash, cold hands and feet, nausea, breathlessness, nightmares and bronchospasm. Selective beta blockers have relatively lesser adverse effects.
- ***Therapeutic uses other than angina include*** hypertension, Cardiac arrhythmias, post myocardial infarction and pheochromocytoma

Calcium channel blockers:

- ***C***alcium is necessary for the excitation contraction coupling in both the cardiac and smooth muscles. Calcium channel blockers appear to involve their interference with the calcium entry into the myocardial and vascular smooth muscle, thus decreasing the availability of the intracellular calcium e.g. nifedipine, felodipine, verapamil and diltiazem.
- ***Other therapeutic uses***: hypertension, acute coronary insufficiency, tachycardia,
- ***Adverse effects:*** flushing nausea/vomiting, headache, Ankle swelling, dizziness, constipation, etc.

❖ **Miscellaneous drugs,e.g. Acetylsalicylic acid**

- Acetylsalicylic acid (aspirin) at low doses given intermittently decreases the synthesis of thromboxne A$_2$ without drastically reducing prostacylin synthesis. Thus, at the doses of 75 mg per day it can produce antiplatelet activity and reduce the risk of myocardial infarction in anginal patients.

Anti - arrhythmics

- **Electrophysiology of cardiac muscle**: the pathophysiological mechanisms responsible for the genesis of cardiac arrhythmias are not clearly understood.
- However, it is generally accepted that cardiac arrhythmias arise as the result of either of
  a) Disorders of impulse formation and/ or
  b) Disorders of impulse conduction.

❖ ***Pharmacotherapy of cardiac arrhythmias***

- Antiarrhythmic drugs are used to prevent or correct cardiac arrhythmias (tachyarrhythmias).
- Drugs used in the treatment of cardiac arrhythmias are traditionally classified into:
  - ✓ **Class (I):** Sodium channel blockers which include quinidine, lidocaine, phenytion, flecainide, etc.
  - ✓ **Class (II):** Beta adrenergic blockers which include propranolol, atenolol, etc.
  - ✓ **Class (III):** Potassium channel blockers e.g. amiodarone, bretylium.
  - ✓ **Class (IV):** Calcium channel blockers e.g. verapamil, etc.
  - ✓ **Class (V):** Digitalis e.g.digoxin.

Class – I drugs

- **Quinidine**: It blocks sodium channel so that there is an increase in threshold for excitability.
  - It is well absorbed orally
  - ***Adverse effects***: It has low therapeutic ratio. Main adverse effects are SA block, cinchonism, severe headache, diplopia and photophobia.
- **Lidocaine,** which is used commonly as a local anaesthetic blocks both open and inactivated sodium channel and decreases automaticity.
  - It is given parenterally.
  - ***Adverse effects***: excessive dose cause massive cardiac arrest, dizziness, drowsiness, seizures, etc.
- **Flecainide:** It is a procainamide analogue and well absorbed orally.
  - It is used in ventricular ectopic beats in patients with normal left ventricular function.

Class –II drugs:

❖Beta-adrenergic receptor blockers

- ***Propranolol:*** Myocardiac sympathetic beta receptor stimulation increases automaticity, enhances A.V. conduction velocity and shortens the refractory period.
- Propranolol can reverse these effects.
- Beta blockers may potentiate the negative inotropic action of other antiarrhythmics.
- ***Therapeutic uses***: This is useful in tachyarrhythmias, in pheochromocytoma and in thyrotoxicosis crisis.
- It is also useful in patients with atrial fibrillation and flutter refractory to digitalis.

Class – III: Potassium channel blockers

- **AMIODARONE:** This drug is used in the treatment of refractory supraventriculat tachyarrhythmias and ventricular tachyarrhythmias.
  - It depresses sinus, atrial and A.V nodal function.
  - The main adverse effects of this drug are anorexia, nausea, abdominal pain, tremor, hallucinations, peripheral neuropathy, A.V. block

Class IV drugs: Calcium channel blockers

- ***Verapamil:*** this drug acts by blocking the movement of calcium ions through the channels.
  - It is absolutely contraindicated in patients on beta blockers, quinidine or disopyramide.
  - It is the drug of choice in case of paroxysmal supraventricular tachycardia for rapid conversion to sinus rhythm.

Class - V drugs:

- **Digoxin** causes shortening of the atrial refractory period with small doses (vagal action) and a prolongation with the larger doses (direct action).
  - It prolongs the effective refractory period of A.V node directly and through the vagus.
  - This action is of major importance in slowing the rapid ventricular rate in patients with atrial fibrillation

Drugs used in hypotensive states and shock

- Antihypotensive drugs or agents are used to elevate a low blood pressure and may be classified as follows:

I. ***Agents intended to increase the volume of blood in activ circulation***.

- ✓ These include intravenous fluids such as whole blood, plasma, plasma components, plasma substitutes and solution of crystalloids

II. ***Vasoconstrictor drugs***

- ✓ these include: Peripherally acting vasoconstrictors which are further divided into sympathomimetic drugs and direct vasoconstrictors.
- ✓ Sympathomimetics used to elevate the blood pressure include adrenaline, noradrenaline, methoxamine, phenylephrine, mephentermine and ephedrine.
- ✓ Direct vasoconstrictors include vasopressin and angiotensin.

Treatment of shock

- Shock is a clinical syndrome characterized by decreased blood supply to tissues.
- Common signs and symptoms include oliguria, heart failure, disorientation, mental confusion, seizures, cold extremities, and comma.
- Most, but not all people in shock are hypotensive.
- The treatment varies with type of shock.
- The choice of drug depends primarily on the *patho-physiology involved.*
- For cardiogenic shock and decreased cardiac out put, ***dopamine*** or other ***cardiotonic*** drug is indicated.
- With severe CHF characterized by decreased CO and high PVR, ***vasodilator drugs*** (nitropruside, nitroglycerine) may be given along with the cardiotonic drug.
- ***Diuretics*** may also be indicated to treat pulmonary congestion if it occurs.

•For anaphylactic shock or neurogenic shock characterized by ***severe vasodilation*** and decreased PVR, a ***vasoconstrictor*** drug (e.g. levarterenol) is the first drug of choice

•For hypovolemic shock, intravenous fluids that replace the type of fluid lost should be given

•For septic shock, appropriate ***antibiotic therapy*** in addition to other ***treatment measures***.