Programme	**B.Pharm**
Course	**Pharmacology II**
Semester	**Vth**
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Unit	**1(Part 1)**
Topic	**Drugs acting on cardiovascular system**
Sub- topic	**Introduction**

- **Drug used in congestive heart failure**
- **Anti-hypertensive drugs**
- **Anti-anginal drugs**
- **Anti-arrythmic drugs**

a. General consideration:-

Hypertension is defined as an elevation of arterial blood pressure above an arbitrarily defined normal value. The American Heart Association defines hypertension as arterial blood pressure higher than 140/90mmHg (based on three measurements at different times). Hypertension may be classified in to three categories, according to the level of diastolic blood pressure:

• Mild hypertension with a diastolic blood pressure between 95-105 mmHg

• Moderate hypertension with a diastolic blood pressure between 105 – 115mmHg

• Severe hypertension with a diastolic blood pressure above 115mmHg.

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.

In order to understand the pathophysiology of hypertensive states and, in turn, the underlying rationale of drug therapy, an appreciation of the systems normally involved in monitoring and regulating blood pressure is required.

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 80-90 % 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).

b. Antihypertensive therapies.

1. Non pharmacological therapy of hypertension

Several non-pharmacological approaches to therapy of hypertension are available.

These include:

• Low sodium chloride diet

• Weight reduction

• Exercise

• Cessation of smoking

• Decrease in excessive consumption of alcohol 53

• Psychological methods (relaxation, meditation …etc)

• Dietary decrease in saturated fats.

The sensitivity of patients differs to these non-pharmacological approaches, but, 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.

2. Pharmacological therapy of hypertension.

Most patients with hypertension require drug treatment to achieve sustained reduction of blood pressure. Currently available drugs lower blood pressure by decreasing either cardiac output (CO) or total peripheral vascular resistance (PVR) or both although changes in one can indirectly affect the other. However, physiological mechanisms tend to oppose a drug – induced reduction of blood pressure.

Anti - hypertensive drugs are classified according to the principal regulatory site or mechanism on which they act. They include:

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.
Diuretics include:
a) Thiazides and related drugs, e.g. hydrochlorthiazide bendrofluazide, chlorthalidone, etc. Initially, thiazide diuretics reduce blood pressure by reducing blood volume and cardiac out put as a result of a pronounced increase in urinary water and electrolyte particularly sodium excretion. With chronic administration (6-8weeks), they decrease blood pressure by decreasing peripheral vascular resistance as the cardiac out put and blood volume return gradually to normal values. Thiazides are appropriate for most patients with mild or moderate hypertension and normal renal and cardiac function.

b) Loop diuretics, e.g. furosemide, ethacrynic acid, etc. Loop diuretics are more potent than thiazides as diuretics. The antihypertensive effect is mainly due to reduction of blood volume. 54 Loop diuretics are indicated in cases of severe hypertension which is associated with renal failure, heart failure or liver cirrhosis.

c) Potassium sparing diuretics, e.g. spironolactone They are used as adjuncts with thiazides or loop diuretics to avoid excessive potassium depletion and to enhance the natriuretic effect of others. The diuretic action of these drugs is weak when administered alone.

B) **Sympathoplegic agents** (Depressants of sympathetic activity). Based on the site or mechanism of action sympathoplegic drugs are divided into:

a) Centrally acting antihypertensive agents e.g. methyldopa, clonidine Centrally acting sympathetic depressants act by stimulating α2 - 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.

II. 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
- 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

1. 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.
2. **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, which 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.

3. **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.

4. **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

1. **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.
2. **Vasodilators**.

   The 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.
3. **Angiotensin converting 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.

III) 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.

1. 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)

2. 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.

3. Calcium channel blockers: calcium 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.

4. Miscellaneous drugs,e.g. Acetylsalicylic acid Acetylsalicylic acid (aspirin) at low doses given intermittently decreases the synthesis of thromboxne A2 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.

IV) 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. 64 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

Diuretics Diuretics are drugs, which increase renal excretion of salt and water: are principally used to remove excessive extracellular fluid from the body. In order to understand the action of diuretics it is important to have some knowledge of the basic processes that take place in the nephron (unit structure of Sites of action of diuretics on renal tubule. Approximately 180 liters of fluid is filtered from the glomerulus into the nephron per day. The normal urine out put is 1-5 liters per day. The remaining is reabsorbed in different areas of nephron. There are three mechanisms involved in urine formation

a) glomerular filtration b) tubular reabsorption

c) Tubular secretion. These processes normally maintain the fluid volume, electrolyte concentration and PH of the body fluids.

Classification of diuretics:- Most of the diuretics used therapeutically act by interfering with sodium reabsorption by the tubules.

The major groups are:

I. Thiazides and related diuretics: e.g. Hydrochlorothiazide chlorthalidone, bendrofluazide, etc.
II. Loop diuretics: e.g. furosemide, ethacrynic acid, etc
III. Potassium sparing diuretics e.g. triamterene, amiloride, spironolactone, etc.
IV. Carbonic anhydrase inhibitors e.g. acetazolamide
V. Osmotic diuretics e.g. mannitol, glycerol

I Thiazide diuretics act by inhibiting NaCl symport at the distal convoluted tubule. They are used in hypertension, edema of hepatic, renal and cardiac origin. Adverse effects: epigastric distress, nausea, vomiting, weakness, fatigue, dizziness, impotence, jaundice, skin rash, hypokalemia, hyperuricemia, hyperglycaemia and visual disturbance.

II Loop diuretics: Loop diuretics like frusemde inhibit Na+ - K – 2Cl symporter in the ascending limb. Adverse effects: Hypokalemia, nausea, anorexia, vomiting epigastric distress, fatigue weakness

muscle cramps, drowsiness. Dizziness, hearing impairment and deafness are usually reversible. Therapeutic uses: acute pulmonary edema, edema of cardiac, hepatic and renal disease. Hypertension, cerebral edema, in drug overdose it can be used to produce forced diuresis to facilitate more rapid elimination of drug.

III Potassium sparing diuretics mechanism of action: Potassium sparing diuretics (spironolactone, triamterene, amiloride) are mild diuretics causing diuresis by increasing the excretion of sodium, calcium and bicarbonate but decrease the excretion of potassium. Adverse effects: G.I. disturbances, dry mouth, rashes confusion, orthostatic hypotension, hyperkalaemia. Hyponatraemia 66 Therapeutic uses: used with conjunction with thiazides or loop diuretics in edema due to, cardiac failure nephrotic syndrome and hepatic disease.

IV Carbonic anhydrase inhibitors: these drugs like acetazolamide inhibit the enzyme carbonic anhydrase in renal tubular cells and lead to increased excretion of bicarbonate, sodium and potassium ions in urine. In eye it results in decrease information of aqueous humor. Therefore these are used in treatment of acute angle glaucoma. Main adverse effects of these agents are drowsiness, hypokalemia, metabolic acidosis and epigastric distress

V Osmotic diuretics: these drugs like mannitol and glycerine (glycerol) are freely filtered at the glomerulus and are relatively inert pharmacologically and undergo limited reabsorption by renal tubule. These are administered to increase significantly the osmolality of plasma and tubular fluid. Some times they produce nausea, vomiting, electrolyte imbalances. They are used in cerebral edema and management of poisoning.

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