CARDIOVASCULAR DRUGS

Antiarrythmics

Arrhythmia is a disturbance or irregularity in heart rate, rhythm, or both, which requires administration of one of antiarrhythmic drugs. An arrhythmia may occur as result of heart disease or from disorder that affects cardiovascular function. Conditions such as emotional stress, hypoxia, and electrolyte imbalance also may trigger an arrhythmia.

Classification

Class I: Membrane stabilizing agents:

- ✓ Moderatly decrease dv/dt of 0 phase: quinidine, procainamide, disopyramide, moricizine
- ✓ Little decrease in dv/dt of 0 phase: lidocaine, mexiletine
- ✓ Marked decrease in dv/dt of 0 phase: Propafenone, flecainide

Class II: Antiadrenergic agents: Propranolol, esmolol, sotalol

Class III: Agents widening AP: Amiodarone, bretylium, dofetilide, ibutilide

Class IV: Calcium channel blockers: Verapamil, diltiazem

QUINIDINE

Quinidine shares all of the pharmacological properties of quinine, including antimalarial, antipyretic, oxytocic, and skeletal muscle relaxant actions.

Pharmacological actions:

1. Cardiac action:-
   - ✓ Automaticity: by inhibiting fast sodium channel during deplorization, it inhibits upstroke AP and depresses diastolic deplorization and hence depresses automaticity of ectopic pacemaker tissues.
   - ✓ Excitability: It depresses the excitability of the cardiac tissue (by increasing the threshold potential) and hence weak ectopic impulse become ineffective.
   - ✓ Conduction velocity: quinidine slows the rate of rise of action potential and thus decrease the conduction velocity in all cardiac tissue (increase ERP, decrease excitability) also contribute to this.
   - ✓ Refractory period: by depressing potassium efflux during repolarization, quinidine prolongs repolarization and hence increase ERP of cardiac tissue. Thus it avoids reentry early or delay after depolarization.
   - ✓ Contractility: it has calcium channel blockade property and hence has negative inotropic effect.

- ✓ ECG effect: increase Q-T interval, decrease in amplitude or inversion of T-wave and depression of ST segment.

2. Extracardiac action: alpha adrenergic property decreases blood pressure, anticholinergic property and possess anti-malaraial activity lesser than quinine.

Pharmacokinetics

Oral bioavailability Almost complete absorption, Onset of action 1–3 hours, Peak response 1–2 hours, Duration of action 6–8 hours, Plasma half-life 6 hours, Primary route of Hepatic; active metabolite, metabolism Primary route of 10–50% renal (unchanged), excretion, Therapeutic serum 2–4 µg /mL concentration.

Preparations and dose

- ✓ Quinidine sulphate tablets and capsules 200-400mg. every 6 hours.
- ✓ Quinidine gluconate injection 200mg. by intramuscular or slow IV injection.

Clinical Uses

- ✓ abolition of premature complexes that have an atrial, A-V junctional, or ventricular origin;
- ✓ restoration of normal sinus rhythm in atrial flutter and atrial fibrillation after controlling ventricular rate with digitalis;
- ✓ maintenance of normal sinus rhythm after electrical conversion of atrial arrhythmias;
- ✓ prophylaxis against arrhythmias associated with electrical countershock;
- ✓ termination of ventricular tachycardia; and
- ✓ Suppression of repetitive tachycardia associated with Wolff-Parkinson-White (WPW) syndrome.

Adverse Effects

Diarrhea, upper gastrointestinal distress, and light-headedness. Other common effects include fatigue, palpitations, headache, anginalike pain, and rash. These effects are dose related and reversible with cessation of therapy. In some patients, quinidine administration may bring on thrombocytopenia due to formation of a plasma protein–quinidine complex that evokes a circulating antibody directed against blood platelet.

Large doses of quinidine can produce a syndrome known as *cinchonism,* characterized by ringing in ears, headache, nausea, visual disturbances or blurred vision, disturbed auditory acuity, and vertigo. Larger doses can produce confusion, delirium, hallucinations, or psychoses. Quinidine can decrease blood glucose concentrations, possibly by inducing insulin secretion.

Contraindications

Complete A-V block with an A-V pacemaker or idioventricular pacemaker; this may be suppressed by quinidine, leading to cardiac arrest. Persons with congenital QT prolongation may develop torsades de pointes tachyarrhythmia and should not be exposed to quinidine.

Owing to negative inotropic action of quinidine, it is contraindicated in congestive heart failure and hypotension. Digitalis intoxication and hyperkalemia can accentuate depression of conduction caused by quinidine.

Myasthenia gravis can be aggravated severely by quinidine's actions at neuromuscular junction. The use of quinidine and quinine should be avoided in patients who previously showed evidence of quinidine-induced thrombocytopenia.

Drug Interactions

Quinidine can increase plasma concentrations of digoxin, which may in turn lead to signs and symptoms of digitalis toxicity.

Gastrointestinal, CNS, or cardiac toxicity associated with elevated digoxin concentrations may occur.

Drugs that have been associated with elevations in quinidine concentrations include acetazolamide, antacids magnesium hydroxide and calcium carbonate, and H_2-receptor antagonist cimetidine. Cimetidine inhibits hepatic metabolism of quinidine.

Phenytoin, rifampin, and barbiturates increase hepatic metabolism of quinidine and reduce its plasma concentrations.

VERAPAMIL

Verapamil, in addition to its use as antiarrhythmic agent, it is employed in management of variant (Prinzmetal's) angina and effort-induced angina pectoris. It selectively inhibits voltage-gated calcium channel that is vital for action potential genesis in slow response myocytes, such as those found in sinoatrial and A-V nodes.

Electrophysiological Actions

- ✓ **Sinoatrial Node:** Spontaneous phase 4 depolarization, a characteristic of normal sinoatrial nodal cells, relies on progressive inhibition of an outward potassium current and an increase in slow inward current that is carried by Na^+ and Ca^+ ions.Verapamil decreases rate of rise and slope of slow diastolic depolarization, the maximal diastolic potential, and membrane potential at peak of depolarization in sinoatrial node.
- ✓ **Atrium:** Verapamil fails to exert any significant electrophysiological effects on atrial muscle.
- ✓ **A-V Node:** Verapamil impairs conduction through A-V node and prolongs A-V nodal refractory period at plasma concentrations that show no effect on His- Purkinje system. The important electrocardiographic change produced by verapamil is prolongation of PR interval, a response consistent with known effects of drug on A-V nodal transmission. Verapamil has no effect on intraatrial and intraventricular conduction. The predominant electrophysiological effect is on A-V conduction proximal to His bundle.
- ✓ **Hemodynamic Effects:** Usual IV doses of verapamil are not associated with marked alterations in arterial blood pressure, peripheral vascular resistance, heart rate, left ventricular end diastolic pressure, or contractility.

Pharmacokinetics

Oral bioavailability 20–35%, Onset of action 1–2 hours, Peak response 1–2 hours, Duration of action 8–10 hours, Plasma half-life 2.8–7.4 hours, Primary route of metabolism Hepatic; active, metabolite, Primary route of excretion Renal (30%, unchanged), and Therapeutic serum concentration 0.125–0.4 µg /mL

Dose: 10mg. thrice daily by oral route.

Clinical Uses

- ✓ It is useful for slowing the ventricular response to atrial tachyarrhythmias, such as atrial flutter and fibrillation.
- ✓ It is also effective in arrhythmias supported by enhanced automaticity, such as ectopic atrial tachycardia and idiopathic left ventricular tachycardia.

Adverse Effects

Orally administered verapamil is well tolerated by most patients. Most complaints are of constipation and gastric discomfort. Other complaints include vertigo, headache, nervousness, and pruritus.

Contraindications

Verapamil must be used with extreme caution or not at all in patients who are receiving β-adrenoceptor blocking agents. Normally, negative chronotropic effect of verapamil will in part be overcome by increase in reflex sympathetic tone. The latter is be prevented by simultaneous administration of a β-adrenoceptor blocking agent, which exaggerates depressant effects of verapamil on heart rate, A-V node conduction, and myocardial contractility. The use in children less than 1 year is controversial.

Anti-hypertensive agents

Hypertension is a disease characterized by abnormally high blood pressure. It may lead to degenerative changes in cerebral, coronary, renal and retinal tissues. Hypertension is classified as:

- ✓ Primary hypertension for which the exact cause is not known.
- ✓ Secondary hypertension which may due to renal, endocrine or vascular lesions.

Antihypertensive drugs are helpful in the treatment of hypertension.

Classification of antihypertensive drugs

1. Drugs acting centrally
   - ✓ Alpha2 adrenergic receptor stimulants: clonidine, methyldopa
   - ✓ Selective imidazole receptor stimulants: moxonidine
2. Drugs acting on the autonomic ganglia: Ganglia blocking agents: trimethaphan
3. Drugs acting on the postganglionic sympathetic nerve endings
   - ✓ Adrenergic neurone blockers: guanethidine, bethanidine, debrisoquine, bretylium
   - ✓ Catecholamine depletors: reserpine
4. Drugs acting on adrenergic receptors
   - ✓ Alpha-adrenergic blocking agents; Phentolamine, phenoxybenzamine, prazosin, indoramin
   - ✓ Beta-adrenergic blocking agents: propronolol, atenolol, metoprolol
   - ✓ Both alpha and beta adrenergic blocking drugs: labetolol
5. Drugs acting directly on vascular smooth muscle:
   - ✓ Arteriolar vasodilators: calcium channel blockers, hydralazine, dizoxide, minoxidil
   - ✓ Arteriolar-venular vasodilators: sodium nitroprusside
6. Potassium channel activators: diazoxide, minoxidil, pincidil, nicorandil
7. Drugs which block rennin-angiotensin aldosterone axis
   - ✓ Those which block rennin release: beta-adrenergic blockers

- ✓ Those which block conversion of angiotensin I to II by inhibiting ACE: captopril, enalapril
- ✓ Those which competitively blocker angiotensin II at vascular receptor sitesL Losartan
- ✓ Those which counter the action of aldosterone: spinolactone

8. Oral diuretics: Thiazides
9. Miscellaneous: metyrosine

PHENOXYBENZAMINE binds covalently to α-receptors, causing irreversible blockade of long duration (14–48 hours or longer). Selective for α_1 receptors but less than prazosin. The drug also inhibits reuptake of released norepinephrine by presynaptic adrenergic nerve terminals. It blocks histamine (H_1), acetylcholine, and serotonin receptors as well as α-receptors.

Pharmacologic actions: It is related to antagonism of α-receptor–mediated events. It attenuates catecholamine-induced vasoconstriction. While phenoxybenzamine causes relatively little fall in blood pressure in normal supine individuals, it reduces blood pressure when sympathetic tone is high, eg, as a result of upright posture or because of reduced blood volume. Cardiac output may be increased because of reflex effects and because of some blockade of presynaptic α_2 receptors in cardiac sympathetic nerves.

Pharmacokinetics

Absorbed after oral administration, bioavailability is low and its kinetic properties are not well known. The drug is usually given orally, starting with low doses of 10–20 mg/d and progressively increasing the dose until desired effect is achieved. A dosage of less than 100 mg/d is sufficient to achieve adequate α-receptor blockade.

Clinical uses

The major use of nonselective agents, phenoxybenzamine is in treatment of pheochromocytoma and in other clinical situations associated with exaggerated release of catecholamines.

Adverse effects

Postural hypotension and tachycardia. Nasal stuffiness and inhibition of ejaculation also occur. It enters central nervous system, it may cause less specific effects, including fatigue, sedation, and nausea.

<u>Calcium channel blockers</u>

a. Phenyl alkylamine: verapamil
b. Benzothiazepine: diltiazem
c. Dihydro puridines: Nifedipine, amlodipine, felodipine, nitrendipine, nimodipine

Actions of calcium channel blockers

Systemic and coronary arteries are influenced by movement of calcium across cell membranes of vascular smooth muscle. The contractions of cardiac and vascular smooth muscle depend on movement of extracellular calcium ions into these walls through specific ion channels. Calcium channel blockers inhibit movement of calcium ions across cell membranes. This results in less calcium available for transmission of nerve impulses. This drug action of calcium channel blockers (slow channel blockers) has effects on heart, including effect on smooth muscle of arteries and arterioles. These drugs dilate coronary arteries and arterioles, which in turn deliver more oxygen to cardiac muscle. Dilation of peripheral arteries reduces workload of heart. An increased blood flow results in increase in oxygen supply to surrounding tissues.

Uses of Calcium channel blockers

- ✓ It is primarily used to prevent anginal pain associated with certain forms of angina, such as vasospastic (Prinzmetal's variant) angina and chronic stable angina. They are not used to abort (stop) anginal pain once it has occurred. When angina is caused by coronary artery spasm, these drugs are recommended when the patient cannot tolerate therapy with the beta-adrenergic blocking drugs or the nitrates.
- ✓ It is used as antianginals.
- ✓ Verapamil affects conduction system of heart and may be used to treat cardiac arrhythmias.
- ✓ Diltiazem, nicardipine, nifedipine, and verapamil also are used in treatment of essential hypertension

Contraindications, precautions, and interactions

- ✓ It is contraindicated in patients who are hypersensitive to drugs and those with sick sinus syndrome, second- or third-degree AV block (except with a functioning pacemaker), hypotension (systolic less than 90 mm Hg), ventricular dysfunction, or cardiogenic shock.
- ✓ It is used cautiously during pregnancy and lactation and in patients with CHF, hypotension, or renal or hepatic impairment.
- ✓ The effects of the calcium channel blockers are increased when administered with cimetidine or ranitidine.
- ✓ A decrease in effectiveness of calcium channel blockers may occur when agents are administered with phenobarbital or phenytoin.
- ✓ Calcium channel blockers have an antiplatelet effect (inhibition of platelet function) when administered with aspirin, causing easy bruising, petechiae (pinpoint purplish red spot caused by intradermal hemorrhage), and bleeding.
- ✓ There is an additive depressive effect on myocardium when calcium channel blockers are administered with β-adrenergic blocking drugs.
- ✓ When calcium channel blockers are administered with digoxin, there is an increased risk for digitalis toxicity.

ATENOLOL

Atenolol, are members of β_1-selective group. These agents may be safer in patients who experience bronchoconstriction in response to propranolol. Since their β_1 selectivity is modest, they should be used with caution, if at all, in patients with history of asthma.

However, in selected patients with chronic obstructive lung disease, the benefits may exceed risks, eg, in patients with myocardial infarction. Beta1-selective antagonists may be preferable in patients with diabetes or peripheral vascular disease when therapy with a β-blocker is required since β2 receptors are probably important in liver (recovery from hypoglycemia) and blood vessels (vasodilation). It is not appreciably metabolized and excreted to a considerable extent in urine. Patients with reduced renal function should receive reduced doses of atenolol. It is claimed that atenolol produces fewer central nervous system-related effects than other more lipid-soluble β-antagonists.

Uses

Angina pectoris, hypertension, myocardial, infarction (MI)

Preparation and dose

Hypertension- 25-50 mg/day PO initially; may be increased to 100 mg/day PO

Angina Pectoris- 50 mg/day PO; after 1 week, may be increased to 100 mg/day PO; some patients may require 200 mg/day

Post Myocardial Infarction (Secondary prevention)- 100 mg PO once daily or divided q12hr for 6-9 days after myocardial infarction (MI)

Adverse effects

Fatigue, hypotension, weakness, blurred vision, stuffy nose, impotence, decreased libido, rash, CHF, bradycardia, pulmonary edema

RESERPINE

Reserpine is prototypical drug interfering with norepinephrine storage. It lowers blood pressure by reducing norepinephrine concentrations in noradrenergic nerves in such a way that less norepinephrine is released during neuron activation. It does not interfere with the release process per se as does guanethidine. Reserpine inhibits only the second uptake process.

Pharmacological Effects

Both cardiac output and peripheral vascular resistance are reduced during long-term therapy with reserpine. Orthostatic hypotension may occur but does not usually cause symptoms. Heart rate and renin secretion fall. Salt and water are retained, which commonly results in "pseudotolerance.".

Therapeutic Uses

At low doses, in combination with diuretics, in treatment of hypertension, in elders. Reserpine is used once daily with a diuretic, and several weeks are necessary to achieve maximum effect.

Dose

For Hypertension

Initial- 0.5 mg daily for 1 or 2 weeks

Maintenance- 0.1-0.25 mg PO qDay

- Use higher dosages cautiously occurrence of mental depression or other adverse reactions may increase

Adverse effects

Sedation and inability to concentrate or perform complex tasks. More serious is psychotic depression can lead to suicide. Reserpine-induced depression may last several months after drug is discontinued. Other effects include nasal stuffiness and exacerbation of peptic ulcer disease, is uncommon with small oral doses.

CLONIDINE

Mechanisms of Action-These agents reduce sympathetic outflow from vasopressor centers in brainstem but allow these centers to retain or even increase their sensitivity to baroreceptor control. Accordingly, the antihypertensive and toxic actions of these drugs are less dependent on posture than are effects of drugs that act directly on peripheral sympathetic neurons.

Pharmacological Actions

- ✓ An acute intravenous injection of clonidine may produce transient pressor response due to stimulation of peripheral vascular α-receptors. The pressor response does not occur after oral administration, because drug's centrally mediated depressor action overrides it.
- ✓ The decrease in blood pressure produced by clonidine correlates better with decreased cardiac output than with reduction in peripheral vascular resistance. The reduction in cardiac output is result of both decreased heart rate and reduced stroke work; the latter effect is probably caused by diminished venous return.
- ✓ Renal blood flow and glomerular filtration are not decreased, although renal resistance is diminished. Like α-methyldopa, it is useful agent for hypertension complicated by renal disease.
- ✓ Plasma renin activity is reduced by clonidine, presumably as a result of a centrally mediated decrease in sympathetic stimulation of juxtaglomerular cells of kidney.

Clinical Uses

- ✓ In mild and moderate hypertension that has not responded adequately to treatment with a diuretic or a β-blocker.
- ✓ A vasodilator can be added to clonidine–diuretic regimen in treatment of resistant forms of hypertension. Such drug combinations can be quite effective, since reflex increases in heart rate and cardiac output that result from vasodilator administration are reduced or negated by clonidine-induced decreases in heart rate and cardiac output.
- ✓ It is useful in patients with renal failure, since its duration of action is not altered by renal disease and it does not compromise renal blood flow.
- ✓ To control diarrhea in diabetic patients with autonomic neuropathy- Stimulation of a_2 receptors in GIT may increase absorption of sodium chloride and fluid and inhibit secretion of bicarbonate.
- ✓ Used in differential diagnosis of patients with hypertension and suspected pheochromocytoma.
- ✓ Useful in selected patients receiving anesthesia because it may decrease the requirement for anesthetic and increase hemodynamic stability
- ✓ Clonidine also is useful in treating and preparing addicted subjects for withdrawal from narcotics, alcohol, and tobacco.
- ✓ Clonidine may help ameliorate some of the adverse sympathetic nervous activity associated with withdrawal from these agents, as well as decrease craving for the drug.

Absorption, Metabolism, and Excretion

Well absorbed after oral administration. Peak plasma levels occur between 2 and 4 hours after drug administration and correlate well with pharmacological activity.The plasma half-life in patients with normal renal function is 12 hours. Urinary excretion of clonidine and its metabolites accounts for almost 90% of administered dose, and fecal excretion accounts for the rest. Approximately 50% of administered dose is excreted unchanged; remainder is oxidatively metabolized in liver.

Adverse Effects

The major adverse effects are dry mouth and sedation. These responses occur in 50% of patients and require drug discontinuation. Sexual dysfunction also may occur. Marked bradycardia occur in some patients. Other adverse effects are related to dose, and their incidence may be lower with transdermal administration, since antihypertensive efficacy may be achieved while avoiding high peak concentrations that occur after given orally. About 15% to 20% of patients develop contact dermatitis

when using clonidine in transdermal system. Withdrawal reactions follow abrupt discontinuation of long-term therapy with clonidine in some hypertensive patients.

POTASSIUM CHANNEL ACTIVATORS

Ex: diazoxide, minoxidil, pincidil, nicorandil

NICORANDIL

It is a novel antianginal drug .

Mechanism of action

These cause dilation of blood vessels by activating potassium channels in vascular smooth muscle. An increase in potassium conductance results in hyperpolarization of cell membrane, which will cause relaxation of vascular smooth muscle.

Adverse reactions

Flushing, palpitation, head ache, dizziness., nausea and vomiting.

Dose: 5 to 20 mg.twice daily.

ACE inhibitors

Captopril is first such agent to be developed for treatment of hypertension. Many of the orally active ACE inhibitors are prodrugs. These include perindopril, quinapril, benazepril, ramipril, lisinopril,moexipril, enalapril, trandolapril, and fosinopril. These drugs have proven to be very useful for treatment of hypertension because of their efficacy and their very favorable profile of adverse effects, which enhances patient adherence.

Mechanism of action

ACE inhibitors may prevent (or inhibit) activity of **angiotensin-converting enzyme,** which converts angiotensin I to angiotensin II, a powerful vasoconstrictor. Both angiotensin I and ACE are **endogenous** substances. The vasoconstricting activity of angiotensin II stimulates secretion of endogenous hormone aldosterone by adrenal cortex. **Aldosterone** promotes retention of sodium and water, which may cause rise in blood pressure. By preventing conversion of angiotensin I to angiotensin II, this chain of events is interrupted, sodium and water are not retained, and blood pressure decreases. The angiotensin II receptor antagonists act to block vasoconstrictor and aldosterone effects of angiotensin II at various receptor sites, resulting in lowering of blood pressure.

CAPTOPRIL

It is an orally effective ACE inhibitor with sulfhydryl moiety that is used in binding to active site of enzyme. Captopril blocks blood pressure responses caused by administration of angiotensin-I and decreases plasma and tissue levels of angiotensin-II.

Pharmacological Actions

- ✓ Treatment with captopril reduces blood pressure in patients with renovascular disease and in patients with essential hypertension.The decrease in arterial pressure is related to reduction in total peripheral resistance.
- ✓ Pharmacological effects of captopril are attributable to the inhibition of angiotensin II synthesis. However, ACE is relatively nonselective enzyme that also catabolizes a family of kinins to

inactive products. Bradykinin, acts as a vasodilator through mechanisms related to production of nitric oxide and prostacyclin by vascular endothelium.

- ✓ ACE inhibitor captopril prevents breakdown of bradykinin.
- ✓ Increases in bradykinin concentrations after administration of ACE inhibitors contribute to therapeutic efficacy of these compounds in treatment of hypertension and CHF.
- ✓ The hypotensive response to captopril is accompanied by fall in plasma aldosterone and angiotensin II levels and increase in plasma renin activity.
- ✓ Serum potassium levels are not affected unless potassium supplements or potassium-sparing diuretics are used concomitantly; results in severe hyperkalemia.
- ✓ There is no baroreflex-associated increase in heart rate, cardiac output, or myocardial contractility in response to the decrease in pressure, because captopril decreases sensitivity of baroreceptor reflex.
- ✓ Captopril enhances cardiac output in patients with congestive heart failure by inducing reduction in ventricular afterload and preload.
- ✓ Converting enzyme inhibitors decrease mass and wall thickness of left ventricle in both normal and hypertrophied myocardium.
- ✓ ACE inhibitors lack metabolic side effects and do not alter serum lipids.

Pharmacokinetics

The onset of action following oral administration of is about 15 minutes, with peak blood levels achieved in 30 to 60 minutes. Its apparent biological half-life is approximately 2 hours, with its antihypertensive effects observed for 6 to 10 hours. The kidneys play major role in inactivation of captopril.

Dose: 25mg. thrice daily as tablets.

Clinical Uses

- ✓ Captopril, as well as other ACE inhibitors, is indicated in treatment of hypertension, congestive heart failure, left ventricular dysfunction after myocardial infarction, and diabetic nephropathy.
- ✓ In treatment of essential hypertension, captopril is considered first choice therapy, either alone or in combination with thiazide diuretic because thiazide-induced hypokalemia is minimized in presence of ACE inhibition, since there is marked decrease in angiotensin II–induced aldosterone release. Decreases in blood pressure are primarily attributed to decreased total peripheral resistance or afterload.
- ✓ It can be used as monotherapy in treatment of congestive heart failure.
- ✓ In treatment of diabetic nephropathy associated with type I insulin-dependent diabetes mellitus, captopril decreases rate of progression of renal insufficiency and retards worsening of renal function.

Adverse Actions

Approximately 10% of patients report dose-related maculopapular rash that often disappears when dosage is reduced. Others are fever, persistent dry cough, initial dose hypotension, and loss of taste that may result in anorexia. These effects are reversed when drug therapy is discontinued. Serious toxicities include proteinuria and glomerulonephritis; less common are leukopenia and agranulocytosis.

Contraindications

Food reduces bioavailability of captopril by 30 to 40%, administration of drug an hour before meals is recommended. All converting enzyme inhibitors are contraindicated in patients with bilateral

renal artery disease or with unilateral renal artery disease and one kidney. Use under these circumstances may result in renal failure or paradoxical malignant hypertension.

Anti-anginals drugs

Angina is a disorder characterized by atherosclerotic plaque formation in coronary arteries, which causes decreased oxygen supply to the heart muscle and results in chest pain or pressure. Any activity that increases workload of heart, such as exercise or simply climbing stairs, can precipitate an angina attack. Antianginal drugs relieve chest pain or pressure by dilating coronary arteries, increasing blood supply to the myocardium.

Classification of anti-anginal drugs

1. Nitrates:
   - ✓ Short acting: Glyceryl trinitrate
   - ✓ Long acting: isosorbide mononitrate, isosorbide dinitrate, Erythrityl tetranitrate, pentaerithrityl tetranitrate,
2. Beta-blockers: propranolol, metoprolol, atenolol,
3. Potassium channel openers: Nicorandil
4. Calcium channel blockers:
   - ✓ Phenyl alkylamine: verapamil
   - ✓ Benzothiazepine: diltiazem
   - ✓ Dihydro puridines: Nifedipine, amlodipine, felodipine, nitrendipine, nimodipine
5. Others: dipyridamole, trimetazidine, oxyphedrine, ranolazine

NITRITES AND NITRATES

Pharmacological actions

1. Blood vessels: These compounds produce direct relaxant effect on arteries, veins and capillaries. There is no involvement of autonomic nerves or receptors. All blood vessels are not equally affected. Vasodilatation is marked in coronary, cerebral and cutaneous vessels. Blood flow is increased, but decrease in blood pressure is minimal
2. Smooth muscle: Nitrites and nitrates produce relaxation of smooth muscles like intestine, biliary tract, ureter and uterus.
3. Eye: These drugs dialate intraocular blood vessels. So ntraocular pressure may be increased.
4. Methemoglobin formation: Nitrites convert hemoglobin to methemoglobin. Methemoglobin combines with cyanides to form non toxic cyanmethemoglobin. So nitrites are useful in the treatment of cyanide poisoning.

Adverse reactions

Head ache, flushing of the face and hypotension leading to dizziness or fainting.

Preparation and dose

Amylnitrite pearls- 0.1 to 0.3 ml by inhalation.
Glyceryl trinitrate tablets- 0.2 to 0.6 mg. sublingually.
Erythrityl tetranitrate tablets- 5 to 10 mg. sublingually.
Pentaerythritol tetranitrate- 10 to 30 mg. orally.

ORGANIC NITRATES

Mechanism of Vasodilator Action

It involves interaction with nitrate receptors, present in vascular smooth muscle. The nitrate receptor possesses sulfhydryl groups, which reduce nitrate to inorganic nitrite and nitric oxide (NO). The formation of nitrosothiols, and free NO, has been proposed to stimulate intracellular soluble guanylate cyclase, which leads to increase in intracellular cyclic guanosine monophosphate formation. The increase in GMP results in vascular smooth muscle relaxation, through inhibition of calcium entry via L-type calcium channels, decreased calcium release from sarcoplasmic reticulum, or via increase in calcium extrusion via sarcolemmal Ca^{2+} ATPase.

Therapeutic Uses

- ✓ **Angina:** Diseases that predispose to angina should be treated as part of a comprehensive therapeutic program with a goal to prolong life. Conditions such as hypertension, anemia, thyrotoxicosis, obesity, heart failure, cardiac arrhythmias, and acute anxiety can precipitate anginal symptoms in many patients. The patient should be asked to stop smoking and overeating; hypertension and hyperlipidemia should be corrected.
- ✓ ***Sublingual Administration.*** Because of its rapid action, long-established efficacy, and low cost, nitroglycerin given sublingually is useful drug. The onset of action is within 1 to 2 minutes, but effects are undetectable by 1 hour after administration. An initial dose of 0.3 mg nitroglycerin often relieves pain within 3 minutes.
- ✓ ***Oral Administration.*** Oral nitrates often are used to provide prophylaxis against anginal episodes in patients who have more than occasional angina. They must be given in sufficient dosage to provide effective plasma levels after first-pass hepatic degradation.
- ✓ ***Cutaneous Administration.*** Application of nitroglycerin ointment can relieve angina, prolong exercise capacity, and reduce ischemic ST-segment depression with exercise for 4 hours or more.
- ✓ ***Transmucosal or Buccal Nitroglycerin.*** This formulation is inserted under upper lip above incisors, where it adheres to gingiva and dissolves gradually. Hemodynamic effects are seen within 2 to 5 minutes, and it is therefore useful for short-term prophylaxis of angina.
- ✓ **Congestive Heart Failure.** The utility of nitrovasodilators to relieve pulmonary congestion and to increase cardiac output in congestive heart failure.
- ✓ **Unstable Angina Pectoris and Non-ST-Segment-Elevation Myocardial Infarction.** The term unstable angina pectoris characterized by an acute or subacute worsening in a patient's anginal symptoms. Along with nitrates and β adrenergic receptor antagonists, antiplatelet agents are used in therapy for acute coronary syndrome. Nitrates are useful both in reducing vasospasm and in reducing myocardial oxygen consumption by decreasing ventricular wall stress. Intravenous administration of nitroglycerin allows high concentrations of drug to be attained rapidly.
- ✓ **Acute Myocardial Infarction** Nitroglycerin is administered to relieve ischemic pain in patients presenting with MI, but evidence that nitrates improve mortality in MI is sparse. Because they reduce ventricular preload through vasodilation, nitrates are effective in relief of pulmonary congestion.
- ✓ **Variant (Prinzmetal) Angina: L**ong-acting nitrates alone are occasionally efficacious in abolishing episodes of variant angina, additional therapy with Ca^{2+} channel blockers is required.

Cardiotonics

CARDIAC GLYCOSIDES are used in treatment of heart failure have been attributed to a positive inotropic effect on failing myocardium and efficacy in controlling ventricular rate response to atrial fibrillation. Cardiac glycosides also modulate autonomic nervous system activity, and this mechanism contributes substantially to their efficacy in management of heart failure. Digitalis which a has two species, namely D*igitalis lanata* and *D. purpurea*. They contain cardiac glycosides digitoxin and digoxin.

Role of sugar moiety in cardiac glycosides

If a sugar molecule is joined together with non-sugar molecule by an ether linkage it is called glycoside. On hydrolysis with mineral acid, all glycosides split up into sugar and non-sugar residues. In cardiac glycosides the sugar part is 1 or 4 molecules of digitoxose while non-sugar part is a steroidal lactone. The pharmacological activity of cardiac glycosides resides in its non-sugar moiety called aglycone. The sugar part, governs the pharmacokinetic characteristics such as lipid solubility and cell permeability.

Mechanisms of Action

Inhibition of Na^+,K^+-ATPase. All cardiac glycosides are potent and highly selective inhibitors of active transport of Na^+ and K^+ across cell membranes. This biological effect is accomplished by binding to a specific site on α subunit of Na^+,K^+-ATPase, the cellular Na^+ pump. The binding of cardiac glycosides to Na^+,K^+-ATPase and inhibition of cellular ion pump is reversible and entropically driven.

Mechanism of Positive Inotropic Effect: Both Na^+ and Ca^{2+} ions enter cardiac muscle cells during each depolarization. Ca^{2+} that enters cell *via* L-type Ca^{2+} channel during depolarization triggers release of stored intracellular Ca^{2+} into cytosol from sarcoplasmic reticulum *via* ryanodine receptor. This Ca^{2+}-induced Ca^{2+} release increases level of cytosolic Ca^{2+} available to interact with contractile proteins, thereby increasing force of contraction. During myocyte repolarization and relaxation, cellular Ca^{2+} is re-sequestered by sarcoplasmic reticular Ca^{2+}-ATPase, and is removed from cell by Na^+-Ca^{2+} exchanger and by sarcolemmal Ca^{2+}-ATPase.

Pharmacological Actions

1. **Cardiac effects**

Mechanical Effects

- ✓ Cardiac glycosides increase contraction of cardiac sarcomere by increasing free calcium concentration in vicinity of contractile proteins during systole.
- ✓ The increase in calcium concentration is result of a two-step process: first, an increase of intracellular sodium concentration because of Na^+/K^+ ATPase inhibition; and second, reduction of calcium expulsion from cell by sodium-calcium exchanger caused by increase in intracellular sodium.
- ✓ The increased cytoplasmic calcium is sequestered by SERCA in SR for later release.

- ✓ The net result of action of therapeutic concentrations of cardiac glycoside is distinctive increase in cardiac contractility.
- ✓ In isolated myocardial preparations, the rate of development of tension and of relaxation is increased, with little or no change in time to peak tension. This effect occurs in both normal and failing myocardium, but in animal or patient, the responses are modified by cardiovascular reflexes and pathophysiology of heart failure.

Electrical Effects

- ✓ The effects of digitalis on electrical properties of heart are mixture of direct and autonomic actions.
- ✓ Direct actions on membranes of cardiac cells follow a well-defined progression: prolongation of action potential, followed by shortening (especially the plateau phase). The decrease in action potential duration is result of increased potassium conductance caused by increased intracellular calcium.

Effects of Digoxin on Electrical Properties of Cardiac Tissues.

Tissue or Variable	**Effects at Therapeutic Dosage**	**Effects at Toxic Dosage**
Sinus node	↓ Rate	↓ Rate
Atrial muscle	↓ Refractory period	↓ Refractory period, arrhythmias
Atrioventricular node	↓ Conduction velocity, ↑refractory period	↑Refractory period, arrhythmias
Purkinje system, ventricular muscle	Slight ↓ refractory period	Extrasystoles, tachycardia, fibrillation
Electrocardiogram	↑ PR interval, ↓ QT interval	Tachycardia, fibrillation, arrest at extremely high dosage

- ✓ At higher concentrations, resting membrane potential is reduced (made less negative) as a result of inhibition of sodium pump and reduced intracellular potassium.
- ✓ As toxicity progresses, oscillatory depolarizing after potentials appear following normally evoked action potentials. The afterpotentials (also known as *delayed afterdepolarizations, DADs*) are associated with overloading of intracellular calcium stores and oscillations in free intracellular calcium ion concentration.
- ✓ When after potentials reach threshold, they elicit action potentials (premature depolarizations or ectopic "beats") that are coupled to preceding normal action potentials.
- ✓ If after potentials in Purkinje conducting system regularly reach threshold in this way, bigeminy will be recorded on electrocardiogram.
- ✓ With further intoxication, each after potential-evoked action potential will itself elicit a supra threshold after potential, and self-sustaining tachycardia will be established. If allowed to

progress, such a tachycardia may deteriorate into fibrillation; in case of ventricular fibrillation, arrhythmia will be rapidly fatal unless corrected.

2. **Autonomic actions** of cardiac glycosides on heart involve both parasympathetic and the sympathetic systems.
   - ✓ In lower portion of dose range, cardioselective parasympathomimetic effects predominate. In fact, these atropine-blockable effects account for significant portion of early electrical effects of digitalis.
   - ✓ This action involves sensitization of baroreceptors, central vagal stimulation, and facilitation of muscarinic transmission at cardiac muscle cell.
   - ✓ Because cholinergic innervation is much richer in atria, these actions affect atrial and atrioventricular nodal function more than Purkinje or ventricular function.
   - ✓ Some cholinomimetic effects are useful in treatment of certain arrhythmias. At toxic levels, sympathetic outflow is increased by digitalis.
   - ✓ This effect is not essential for typical digitalis toxicity but sensitizes myocardium and exaggerates all toxic effects of drug.
   - ✓ The most common cardiac manifestations of digitalis toxicity include atrioventricular junctional rhythm, premature ventricular depolarizations, bigeminal rhythm, and second-degree atrioventricular blockade. However, it is claimed that digitalis can cause virtually any arrhythmia.

3. Effects on other organs

- ✓ Cardiac glycosides affect all excitable tissues, including smooth muscle and central nervous system. The gastrointestinal tract is most common site of digitalis toxicity outside heart. The effects include anorexia, nausea, vomiting, and diarrhea. This toxicity may be partially caused by direct effects on gastrointestinal tract but is result of CNS actions.
- ✓ Central nervous system effects include vagal and chemoreceptor trigger zone stimulation. Less often, disorientation and hallucinations—in elders—and visual disturbances are noted. The latter effect may include aberrations of color perception. Gynecomastia is a rare effect reported in men taking digitalis.

Absorption, distribution, metabolism and excretion

Digoxin is absorbed 65–80% after oral administration. Absorption of other glycosides varies from zero to nearly 100%. Once present in blood, all cardiac glycosides are widely distributed to tissues, including CNS. Digoxin is not extensively metabolized in humans; almost two thirds is excreted unchanged by kidneys. Its renal clearance is proportionate to creatinine clearance.

Clinical uses

- ✓ Digoxin therapy is indicated in patients with severe left ventricular systolic dysfunction after initation of diuretic and vasodilatation therapy. Digoxin is not indicated in patients with diastolic or right-sided hear failure.

- ✓ **Paroxysmal supraventriular tachycardia**: it is common arrhythmia due to recentry phenomenon taking place at SA or AV node. They frequently respond to digitalis, because of reflex vagal activation which slows conduction of impulses.
- ✓ **Congestive heart failure**: digitalis is a drug of choice for low output heart failure due to HT, IHD, or arrhythmias.
- ✓ **Dilated heart:** digitalis is preferred drug for patient having dilated heart and low ejection fractionas it is helpful in restoring cardiac compensation.
- ✓ It is used to treat HF and atrial fibrillation. Atrial fibrillation is cardiac arrhythmia characterized by rapid contractions of atrial myocardium, resulting in an irregular and often rapid ventricular rate.

Adverse Actions

- ✓ Cardiac side effects: include bradycardia, partial or complete heart block, atrial or ventricular extrasystoles, coupled beats, ventricular fibrillation and fatal cardia arrhythmias.

- ✓ Extra cardiac side effects:
- ✓ GIT: anorexia, nausea, vomiting, diarrhea, and abdominal cramps.

- ✓ CNS: headache, fatigue, neuralgia, blurred vision, loss of color perception.

- ✓ Endocrinal: gyanecomastia in males.

Contraindications

It is contraindicated in patients with known hypersensitivity, ventricular failure, ventricular tachycardia, or AV block and in the presence of digitalis toxicity.

Precautions

Given cautiously in patients with electrolyte imbalance (especially hypokalemia, hypocalcemia, and hypomagnesemia), severe carditis, heart block, myocardial infarction, severe pulmonary disease, acute glomerulonephritis, and impaired renal or hepatic function.

Hypolipidemics

These are the drugs which lower the levels of lipids and lipoproteins in blood. Thus they prevent the narrowing of blood vessels like cerebral and coronary arteries.

Dyslipidaemia means abnormalities of plasma lipids and lipoprotein concentration. These may manifest in following ways:

- o Elevated total cholesterol levels.
- o Elevated low density lipoprotein cholesterol levels.
- o Elevated triglyceride levels.
- o Decrease high density lipoprotein cholesterol levels.

Drugs Classification

- ✓ HMG-CoA reductase inhibitors (statin): Lovastatin, simvastatin, pravastatin, atorvastatin, rosuvastatin.

- ✓ Bile acid sequestrants: cholestyramine, colestipol
- ✓ Activate lipoprotein lipase: clofibrate, gemfibrozil, bezafubrate, fenofibrate
- ✓ Inhibit lipolysis and triglyceride synthesis: Nicotinic acid
- ✓ Others: ezetimibe, gugulipid.

EZETIMIBE

Ezetimibe is first compound approved for lowering total and LDL-C levels that inhibits cholesterol absorption by enterocytes in small intestine. It lowers LDL-C levels by about 18% and is used primarily as adjunctive therapy with statins.

Mechanism of Action

It is selective inhibitor of intestinal absorption of cholesterol and phytosterols. A transport protein, NPC1L1, appears to be target of drug. It is effective even in absence of dietary cholesterol because it inhibits reabsorption of cholesterol excreted in bile.

Absorption, Fate, and Excretion

Ezetimibe is highly water insoluble, precluding studies of its bioavailability. After ingestion, it is glucuronidated in intestinal epithelium, absorbed, and enters an enterohepatic recirculation. Excreted in feces and urine. Bile acid sequestrants inhibit absorption of ezetimibe, and two agents should not be administered together. **Dose :**10 mg orally once a day

Adverse Effects and Drug Interactions

Allergic reactions, but no specific adverse effects have not been observed in patients taking ezetimibe. The safety of ezetimibe during pregnancy has not been established. *Since all statins are contraindicated in pregnant and nursing women, combination products containing ezetimibe and statin should not be used by women in absence of contraception.*

Therapeutic Uses

Average reduction in LDL cholesterol with ezetimibe alone in patients with primary hypercholesterolemia is about 18%, with minimal increases in HDL cholesterol. It is also effective in patients with phytosterolemia. Ezetimibe is synergistic with reductase inhibitors, producing decrements as great as 25% in LDL cholesterol beyond that achieved with the reductase inhibitor alone.

Treatment with drug combinations

Reductase Inhibitors & Ezetimibe: This combination is highly synergistic in treating primary hypercholesterolemia and has some use in the treatment of patients with homozygous familial hypercholesterolemia who have some receptor function.

Ternary Combination of Resins, Ezetimibe, Niacin, & Reductase Inhibitors: These agents act in complementary fashion to normalize cholesterol in patients with severe disorders involving elevated LDL. The effects are sustained, and little compound toxicity has been observed. Effective doses of individual drugs may be lower than when each is used alone—eg. niacin may substantially increase effects of other agents.

SIMVASTATIN

It is an antihyperlipidemic drugs, it is an **HMG-CoA reductase inhibitors.** HMG-CoA (3-hydroxy-3-methyglutaryl coenzyme A) reductase is an enzyme that is **catalyst** in manufacture of cholesterol. These drugs appear to have one of two activities, namely, inhibiting manufacture of cholesterol or promoting breakdown of cholesterol. This drug activity lowers blood levels of cholesterol and serum triglycerides and increases blood levels of HDLs.

Uses

It is used along with a diet restricted in saturated fat and cholesterol, are used to treat hyperlipidemia when diet and other nonpharmacologic treatments alone have not resulted in lowered cholesterol levels.

Dose

Initial dose- 10 to 20 mg orally once a day.
High risk patients may initate at 40 mg orally once a day.
Maintenance dose- 5 to 40 mg orally once a day.
Maximum dose : 40 mg/ day

Adverse effects

Adverse effects are mild and transient and do not require discontinuing therapy. Others are nausea, vomiting, constipation, abdominal pain or cramps, and headache. A rare, but more serious, adverse reaction is rhabdomyolysis.