PHARMACOGOLOGY-II- BP503T

UNIT : 1(Cardiovascular system)

CLASS:1

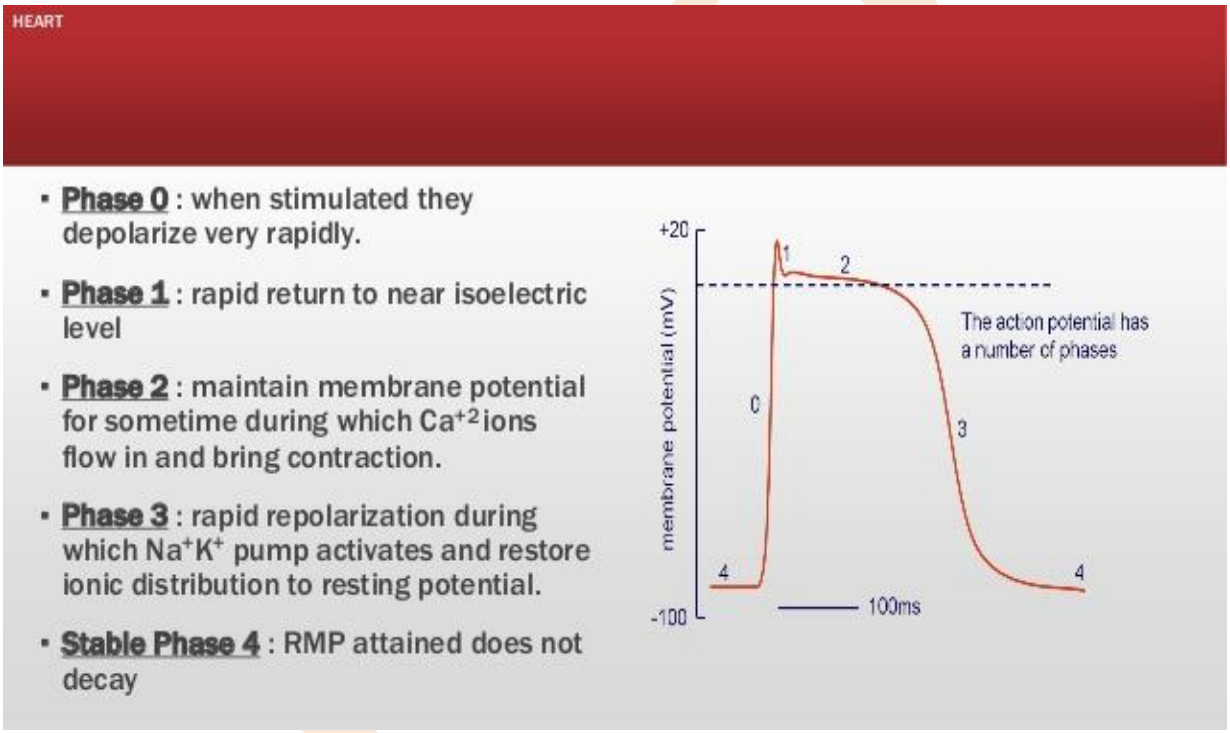
TOPIC: CARDIOVASCULAR SYSTEM Introduction.

The action potential of an idealised cardiac muscle cell and is divided into five:
phases: 0 (fast depolarisation), 1 (partial repolarisation), 2 (plateau), 3 (repolarisation) and 4 (pacemaker).
▼ Ionic mechanisms underlying these phases can be summarised as
follows.
Phase 0, rapid depolarisation, occurs when the membrane potential reaches a critical firing threshold (about −60 mV), at which the inward current of Na+ flowing through the voltage-dependent sodium channels becomes large enough to produce a regenerative ('all-or-nothing') depolarisation. This mechanism is the same as that responsible for action potential generation in neurons.
Activation of sodium channels by membrane depolarisation is transient, and if the membrane remains depolarised for more than a few milliseconds, they close again (inactivation). They are therefore closed during the plateau of the action potential and remain unavailable for the initiation of another action potential until the membrane repolarises.

Phase 1, partial repolarisation, occurs as the Na+ current is inactivated.
There may also be a transient voltage-sensitive outward current.
Phase 2, the *plateau*, results from an inward Ca2+ current. Calcium channels show a pattern of voltage-sensitive activation and inactivation qualitatively similar to sodium channels, but with a much slower time course. The plateau is assisted by a special property of the cardiac muscle membrane known as *inward-going rectification*, which means that the K+ conductance falls to a low level when the membrane is depolarised. Because of this, there is little tendency for
outward K+ current to restore the resting membrane potential during the plateau, so a relatively small inward Ca2+ current suffices to maintain the plateau. A persistent sodium current (*I*Nap) also contributes to the plateau; it is a major contributor to ischaemic arrhythmias, and is a drug target (see p. 260).
Phase 3, repolarisation, occurs as the Ca2+ current inactivates and a delayed outwardly rectifying K+ current (analogous to, but much slower than, the K+ current that causes repolarisation in nerve fibres; activates, causing outward K+ current. This is augmented by another K+ current, which is activated by high intracellular Ca2+ concentrations, [Ca2+]i during the plateau, and sometimes also by other K+ currents, including one through channels activated by acetylcholine (see p. 253) and another that is activated by arachidonic acid, which is liberated under pathological conditions such as myocardial infarction.
Phase 4, the *pacemaker potential*, is a gradual depolarisation during diastole. Pacemaker activity is normally found only in nodal and conducting tissue. The pacemaker potential is caused by a combination of increasing inward currents and declining outward currents during diastole. It is usually most rapid in cells of the SA node, which therefore acts as pacemaker for the whole heart. Cells in the SA node have a greater background conductance to Na+ than do atrial or

ventricular myocytes, leading to a greater background inward current. In addition, inactivation of voltage-dependent calcium channels wears off during diastole, resulting in increasing inward Ca2+ current during late diastole. Activation of T-type calcium channels during late diastole contributes to pacemaker activity in the SA node. The negative membrane potential early in diastole activates a cation channel that is permeable to Na+ and K+, giving rise to another inward current, called *I*f.1 An inhibitor of this current, **ivabradine**, slows the heart and is used therapeutically (see below).

Several voltage- and time-dependent outward currents play a part as well: delayed rectifier K+ current (*I*K), which is activated during the action potential, is turned off by the negative membrane potential early in diastole. Current from the electrogenic Na+/K+ pump also contributes to the outward current during the pacemaker potential.



PHARMACOGOLOGY-II- BP503T

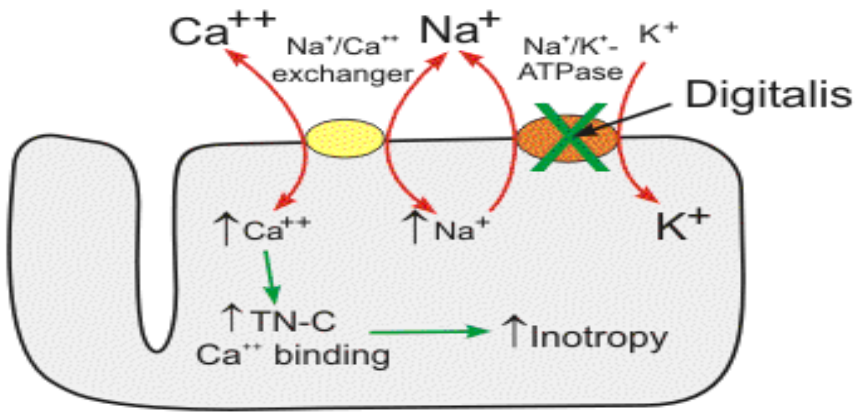
UNIT : 1(Cardiovascular system)

CLASS: 2

TOPIC: Congestive heart failure: DIGITALIS:

Heart failure is an extremely serious cardiac condition associated with high mortality. The fundamental physiology defect in heart failure is a **decrease in cardiac output** relative to the needs of the body, and the major manifestations are dyspnea and fatigue.

Mechanism of action: Digitalis compounds are potent inhibitors of cellular Na^+/K^+-ATPase. This ion transport system moves sodium ions out of the cell and brings potassium ions into the cell. This transport function is necessary for cell survival because sodium diffusion into the cell and potassium diffusion out of the cell down their concentration gradients would reduce their concentration differences (gradients) across the cell membrane over time. Hence, digitalis decreases the force of contraction of heart.



Pharmacological actions of Digitalis – HEART

Overall actions:

1. Direct Effects - Myocardial contractility and electrophysiology
2. Vagomimetic effect
3. Reflex action – alteration of hemodynamic
4. CNS effects – altering sympathetic activity

Force of Contraction:

- Dose dependent increase in force of contraction in failing heart – positive inotropic effect
- Increased velocity of tension development and higher peak tension
- Systole is shortened and prolonged diastole
- In Normal Heart – what happens ??

Digitalis – Common Drug interactions

- **Diuretics:** Hypokalaemia (K+ supplementation required)
- **Calcium:** synergizes with digitalis
- **Adrenergic drugs:** arrhythmia
- **Propranolol and Ca++ channel blockers:** depress AV conduction and oppose positive ionotropic effects
- **Metoclopramide, sucralfate and antacids** – reduced absorption

Cardiac glycosides - Digoxin

- **Pharmacokinetics:**
  - — Absorbed orally. Absorption varies from zero to nearly 100%.
  - — Distributed widely to tissues, including the central nervous system.
  - — Digoxin is not extensively metabolized in humans
  - — Almost two thirds is excreted unchanged by the kidneys. Its renal clearance is proportional to creatinine clearance, and the half-life is 36—40 hours in patients with normal renal function.

Digitalis – Adverse effects

Cardiac: All Arrhythmias

- **Tachyarrythmias:** Heart rate abnormally increased due to prolong diuretic and digitalis therapy (K depletion) – Potassium chloride 20 m.mol IV/hr or orally
  - Digitalis toxicity – don't give K+
  - Serum K+ estimation
- **Ventricular arrhythmia:** Excessive ventricular automaticity: Lidocaine IV (or Phenyton)
- **PSVT:** Propranolol IV or Adenosine
- **AV block:** Atropine - 0.6 to 1.2 mg IM

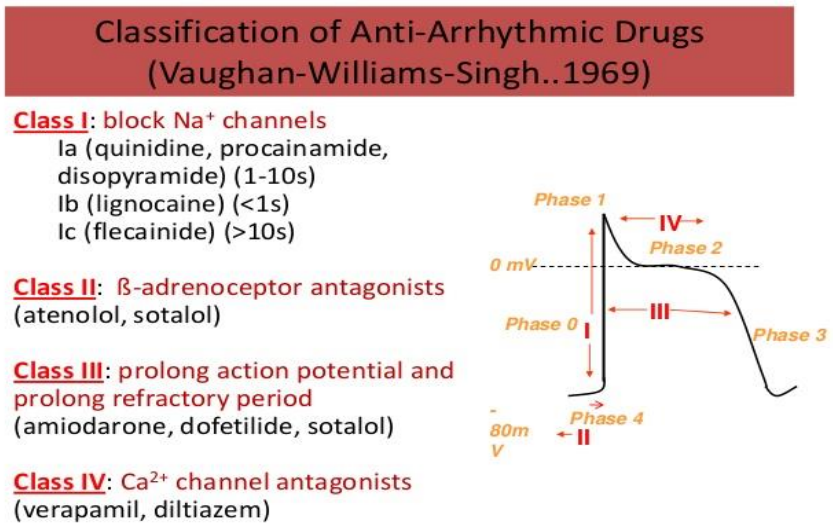
PHARMACOGOLOGY-II- BP503T

UNIT : 1(Cardiovascular system)

CLASS: 3

TOPIC: Anti-arrythmic drugs:

Antiarrhythmic agents, also known as **cardiac dysrhythmia medications**, are a group of pharmaceuticals that are used to suppress abnormal rhythms of the heart (cardiac arrhythmias), such as atrial fibrillation, atrial flutter, ventricular tachycardia, and ventricular fibrillation.



Class I: drugs that block voltage-sensitive sodium channels. They are subdivided: Ia, Ib and Ic.

- **Class II: β-adrenoceptor antagonists.**
- **Class III: drugs that substantially prolong the cardiac action potential.**

Class IV: calcium antagonists

Class I drugs

Class I drugs block sodium channels, just as local anaesthetics

Class Ia, **quinidine** and **procainamide**: Have different effects from many of the more recently developed drugs, even though all share the same basic mechanism of action.

CLASS I a
QUINIDINE

pharmacological actions :

Actions on A.N.S. (indirect) :

1- Anticholinergic effect

↓

Increase conduction through the A.V. node

(risk of ventricular tachycardia)

2- α-adrenergic blocking effect

↓

may cause vasodilatation & reflex sinus tachycardia

(seen more after I.V. dose)

Quinidine (Cont.)

- **Other actions:**
- Anti-cholinergic (vagolytic effect), ↑ AV-conduction
- This increases ventricular rate in atrial flutter
- Propranolol or verapamil is added to reduce this effect
- **Uses:**
- Supra-ventricular & ventricular tachycardia (given oral & IV)
- **Adverse effects:**
- **CVS:** Bradycardia & cardiac depression
  Quinidine syncope (a-blocking effect)
  Thrombocytopenia (immune reaction)
- **GI:** nausea, vomiting & diarrhea
- **Cinchonism:** tinnitis, vertigo & headache
- Drug interaction: ↑ toxicity of digoxin, due to ↓ renal excretion

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Quinidine

- *Clinical Pharmacokinetics*
- well absorbed
- 80% bound to plasma proteins (albumin)
- extensive hepatic oxidative metabolism
- 3-hydroxyquinidine,
- is nearly as potent as quinidine in blocking cardiac Na^+ channels and prolonging cardiac action potentials.

Class II drugs

Class II drugs comprise the β-adrenoceptor antagonists (e.g. **metoprolol**).
Adrenaline can cause dysrhythmias by its effects on the pacemaker potential and on the slow inward Ca2+ current. Ventricular dysrhythmias following myocardial infarction are partly the result of increased sympathetic activity, providing a rationale for using β-adrenoceptor antagonists in this setting. AV conduction depends critically on sympathetic activity; β-adrenoceptor antagonists increase the refractory period of the AV node and can therefore prevent recurrent attacks of supraventricular tachycardia (SVT). The β-adrenoceptor antagonists are also used to prevent paroxysmal attacks of atrial fibrillation when these occur in the setting of sympathetic activation.

Class III drugs: The class III category was originally based **Class III drugs.** The class III category was originally based on the unusual behaviour of a single drug, **amiodarone** (see p. 258), although others with similar properties (e.g. **sotalol**) have since been described.

Lidocaine (class Ib)

Lidocaine, also well known as a local anaesthetic, is given by intravenous infusion, to treat and prevent ventricular dysrhythmias in the immediate aftermath of myocardial infarction. It is almost completely extracted from the portal circulation by hepatic first-pass metabolism, and so cannot usefully be swallowed (although if administered into the mouth to produce local anaesthesia it can be absorbed directly into the systemic circulation and cause systemic effects). Its plasma half-life is normally about 2 h, but its elimination is slowed if hepatic blood flow is reduced, for example by reduced cardiac output following myocardial infarction or by drugs that reduce cardiac output (e.g. β-adrenoceptor antagonists).

The adverse effects of lidocaine are mainly due to its actions on the central nervous system and include drowsiness, disorientation and convulsions.

β-Adrenoceptor antagonists (class II)

β-Adrenoceptor antagonists are metaprolol,propanalol. Their clinical use for rhythm disorders is shown in the clinical box. **Propranolol**, like several other drugs of this type, has some class I action in addition to blocking β adrenoceptors. This may contribute to its antidysrhythmic effects, although probably not very much, because an isomer with little β-antagonist activity has little antidysrhythmic activity, despite similar activity as a class I agent.
Adverse effects include worsening bronchospasm in patients with asthma, a negative inotropic effect, bradycardia and fatigue. It was hoped that the use of β1-selective drugs (e.g. **metoprolol**, **atenolol**) would reduce the risk of bronchospasm, but their selectivity is insufficient to achieve this goal in clinical practice, although the once-a-day convenience of several such drugs has led to their widespread use in patients without lung disease.

Beta-blockers are used for treating hypertension, angina, myocardial infarction, arrhythmias and heart failure.

PHARMACOGOLOGY-II- BP503T

UNIT : 1(Cardiovascular system)

CLASS: 4

TOPIC: Anti-arrythmic drugs:

Class III

Amiodarone is highly effective at suppressing dysrhythmias (see the clinical box below). Like other drugs that interfere with cardiac repolarisation, it is important to monitor plasma electrolyte concentrations (especially of K+).

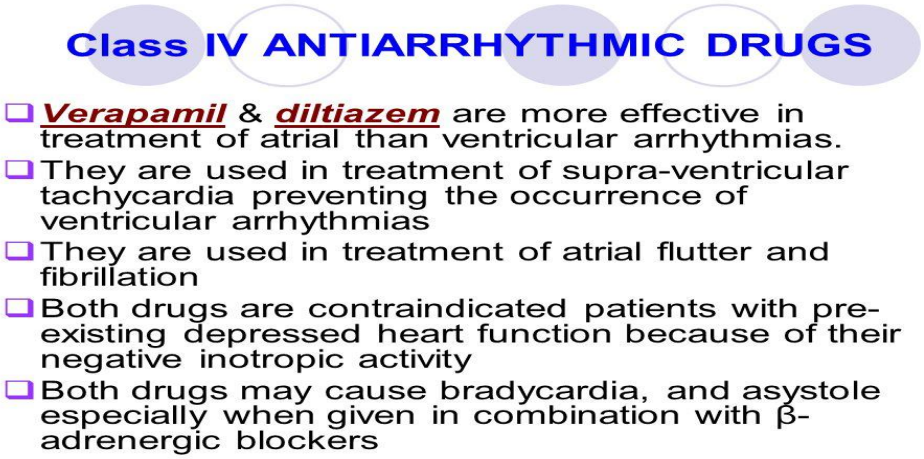
Adverse effects:

Photosensitive skin rashes and a slate-grey/bluish discoloration of the skin;

Thyroid abnormalities (hypo- and hyper-, connected with its iodine content);

Pulmonary fibrosis, corneal deposits; and neurological and gastrointestinal disturbances, including hepatitis.

Sotalol is a non-selective β-adrenoceptor antagonist, this activity residing in the L isomer. Unlike other β antagonists, it prolongs the cardiac action potential and the QT interval by delaying the slow outward K+ current



Drug kinetics: from notes.

Clinical uses of class IV antidysrhythmic drugs: • Verapamil is the main drug.

It is used: – to prevent recurrence of paroxysmal supraventricular tachycardia (SVT) – to reduce the ventricular rate in patients with atrial fibrillation, provided they do not have Wolff–Parkinson–White or a related disorder.

Verapamil was previously given intravenously to terminate SVT; it is now seldom used for this because adenosine is safer.

PHARMACOGOLOGY-II- BP503T

UNIT : 1(Cardiovascualar system)

CLASS: 5

TOPIC: ANGINA PECTORIS

Angina pectoris is the medical term for chest pain or discomfort due to coronary heart disease. It occurs when the heart muscle doesn't get as much blood as it needs. This usually happens because one or more of the heart's arteries is narrowed or blocked, also called ischemia.

Types of Angina

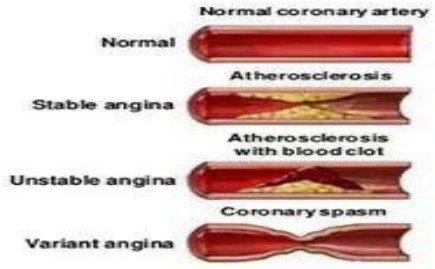
Knowing the types of angina and how they differ is important.

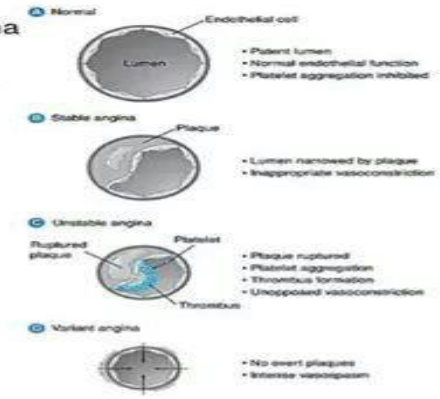
- Stable Angina / Angina Pectoris
- Unstable Angina
- Variant (Prinzmetal) Angina
- Microvascular Angina

Stable angina	***Variant angina***	***Unstble angina***
▪ Typical, classic, Common angina ▪ ***M***ost common angina ▪ Occurs during emotional stress, heavy exercise, ▪ Esily predictable ▪ Treating more rest,nitroglycern ▪ Also due to ***atherosclerosis***	▪ Prize metal angina ▪ Occurs in rest also ▪ Due to Spasm of coronary artery	▪ Uncommon or atypicaltype ▪ Occurs in exercise and also during rest ▪ Prolanged angina may lead to ***Miocardial infraction*** ▪ Unpredictable

Three types of angina

- **Stable angina**/Classic angina/Effort angina
- **Unstable angina**/Crescendo angina
- **Variant angina**/Prinzmetal angina



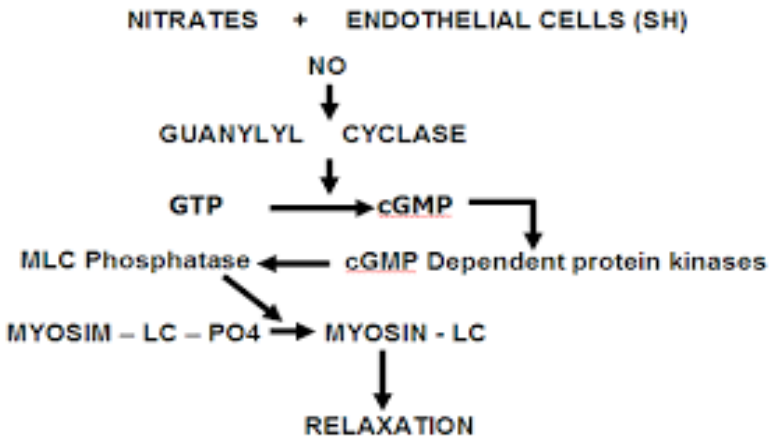


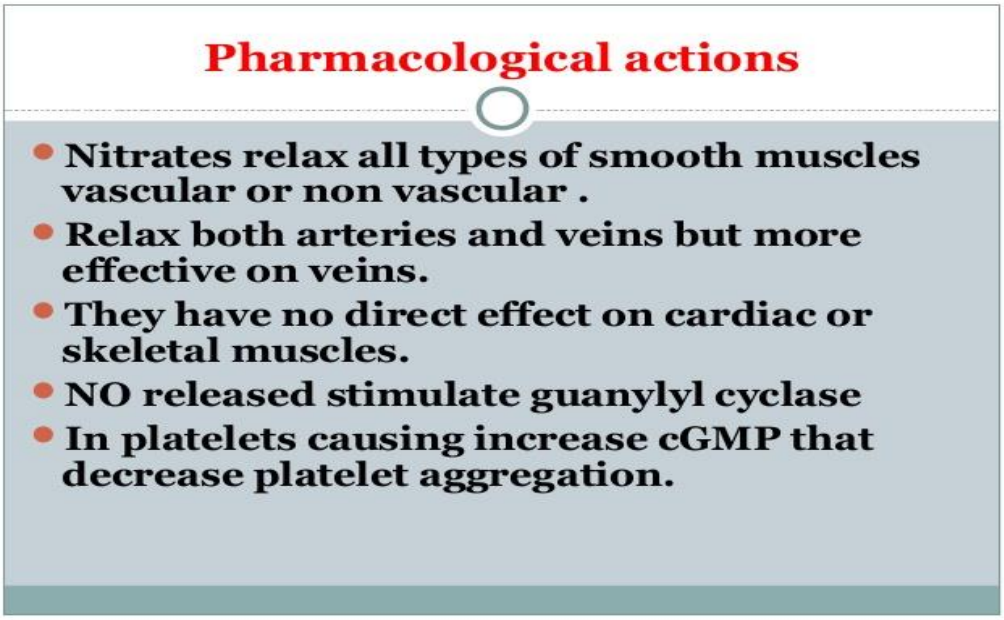
CLASSIFICATION

- **1. NITRATES –** SHORT ACTING -Glyceryl trinitrate
  LONG ACTING - Isosorbide dinitrate, Isosorbide mononitrate
- **2. BETABLOCKERS** - Propranolol, metoprolol, Atenolol
- **3. CALCIUM CHANNEL BLOCKERS** - Verapamil, Diltiazem, Nifedipine, Amlodipine, Nitrendipine
- **4. POTASSIUM CHANNEL OPENER** - Nicorandil
- **5. OTHERS –** Trimetazidine, Dipyridamole, Oxyfedrine

Nitrates:

M.O.A:





PHARMACOGOLOGY-II- BP503T

UNIT : 1(Cardiovascular system)

CLASS: 6

TOPIC: ANGINA PECTORIS

Nitrates & Nitrites

- **Preparations :**
- **1- Short acting:**
- **Start within few minutes** and total duration of action 15-30 minutes.
- **A) Nitroglycerine (Glyceryl trinitrate)**
- **Used as sublingual tablets.**
- **B) Isosorbide dinitrate**
- **As sublingual spray.**
- **C) Amyl nitrite**
  - **Inhalation**

Long acting

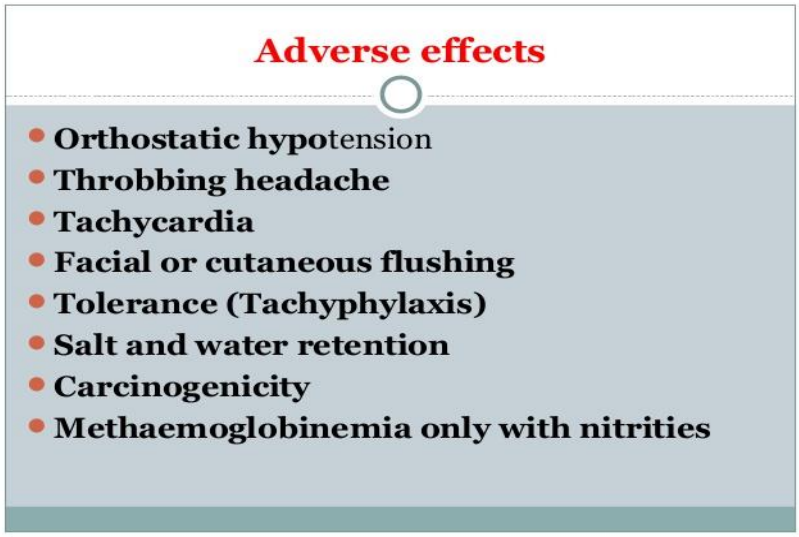
- **Nitroglycerine, Isosorbide dinitrate,**
- **Isosorbide mononitrate,Erythrityl –**
- **Tetranitrate.**
  - Action of all start withen hours and continue for hours .
- **They are given : Orally,Ointment,Buccal,Transdermal patch,Parenteral.**

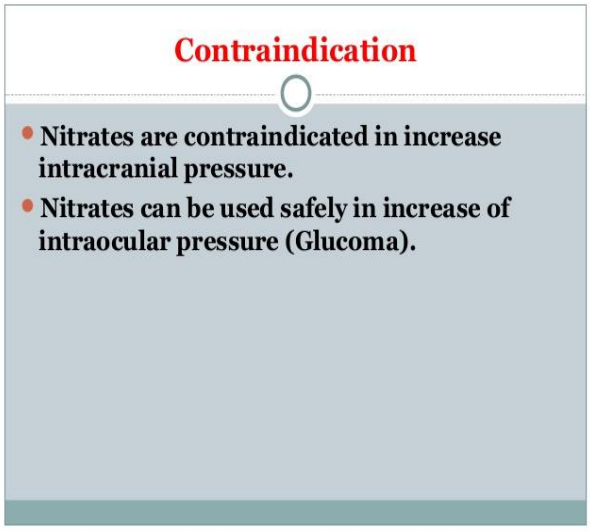
Pharmacological actions

- Nitrates relax all types of smooth muscles vascular or non vascular .
- Relax both arteries and veins but more effective on veins.
- They have no direct effect on cardiac or skeletal muscles.
- NO released stimulate guanylyl cyclase
- In platelets causing increase cGMP that decrease platelet aggregation.

Clinical uses

- Short acting for acute attacks
  Long acting for prophylactic.
- Treatment of all types of angina .



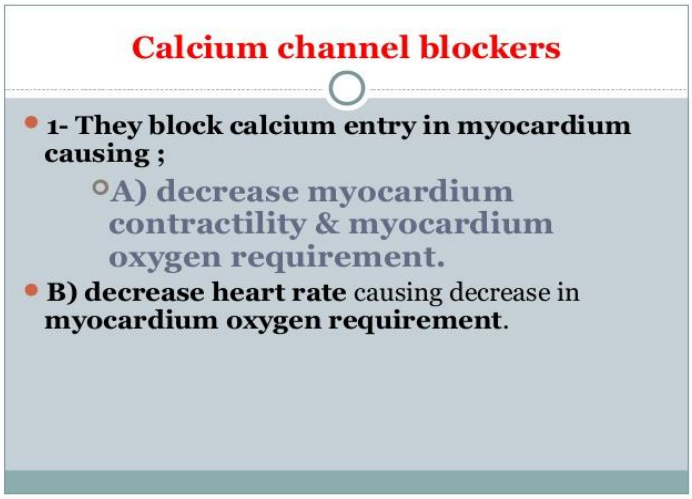


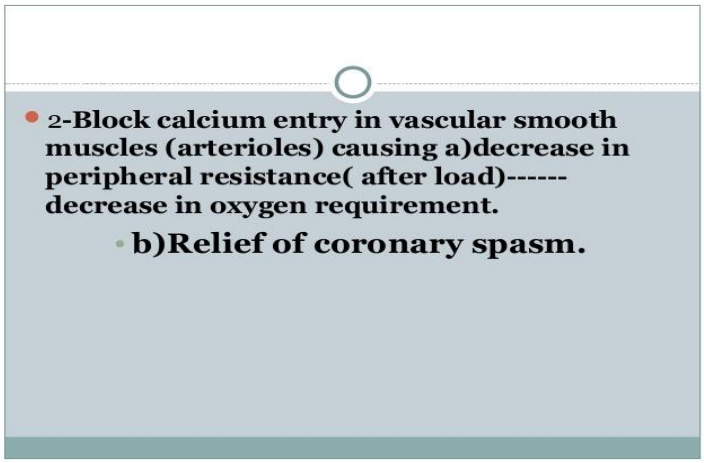
PHARMACOGOLOGY-II- BP503T

UNIT : 1(Cardiovascualar system)

CLASS: 7

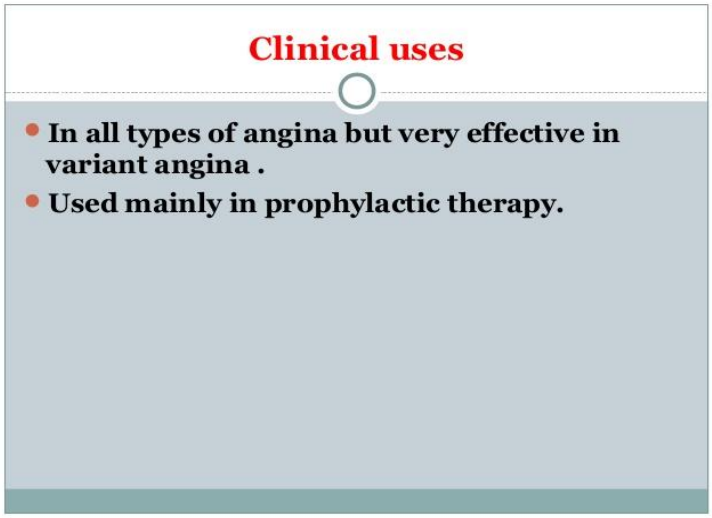
TOPIC: ANGINA PECTORIS





MO.A of calcium channel blockers:

Block calcium entry in vascular smooth muscle.

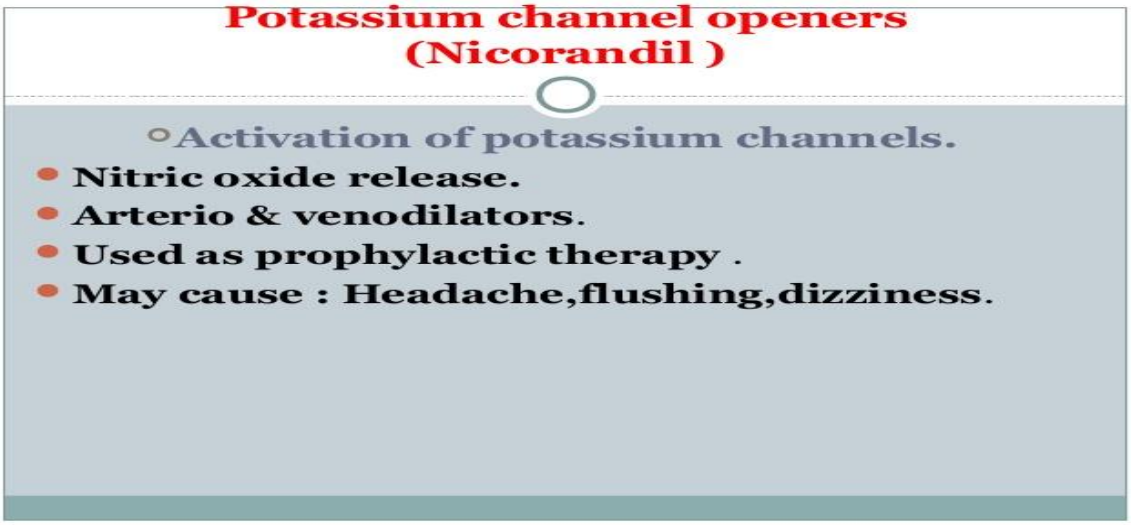


β-Adrenoreceptor blocking drugs

- They are not vasodilators
- They are used in treatment of angina :
- They decrease both heart rate & myocardial contractility that decrease in myocardial oxygen requirement at rest & in exercise so improve exercise tolerance.

Clinical uses

- They are effective in the prophylactic treatment of classic & unstable angina.
- They are not used in variant angina.
- They are effective in treatment of silent or ambulatory angina (no pain).
- Decrease mortality of patients with recent myocardial infarction.



Remaining from notes and text book.

PHARMACOGOLOGY-II- BP503T

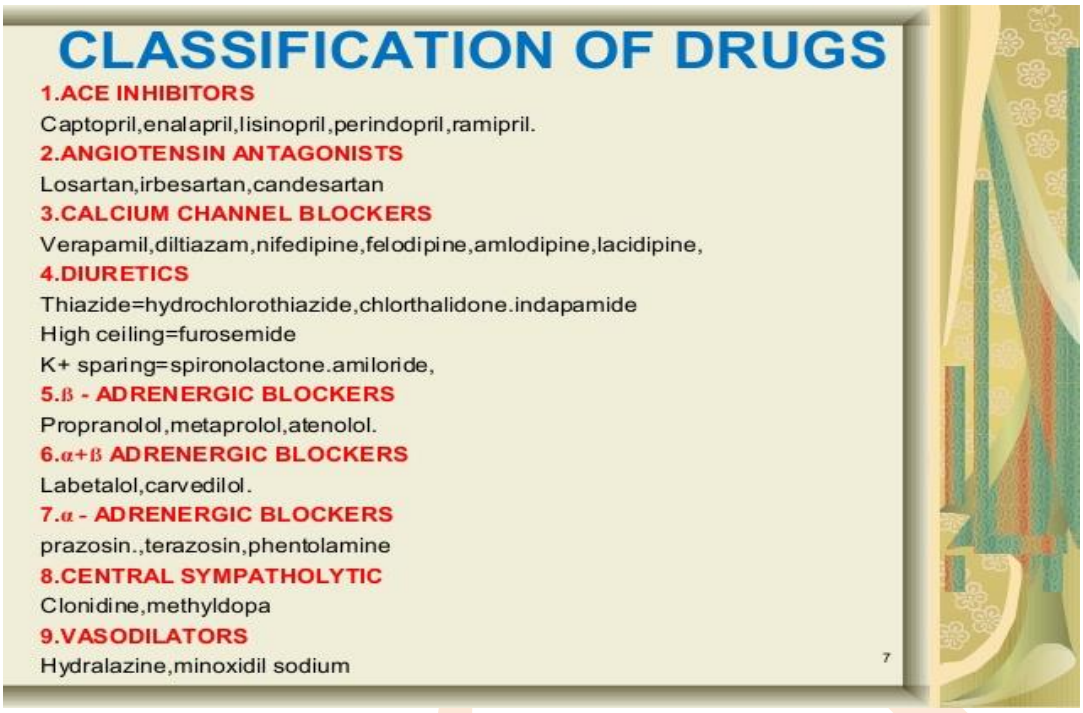
UNIT : 1(Cardiovascular system)

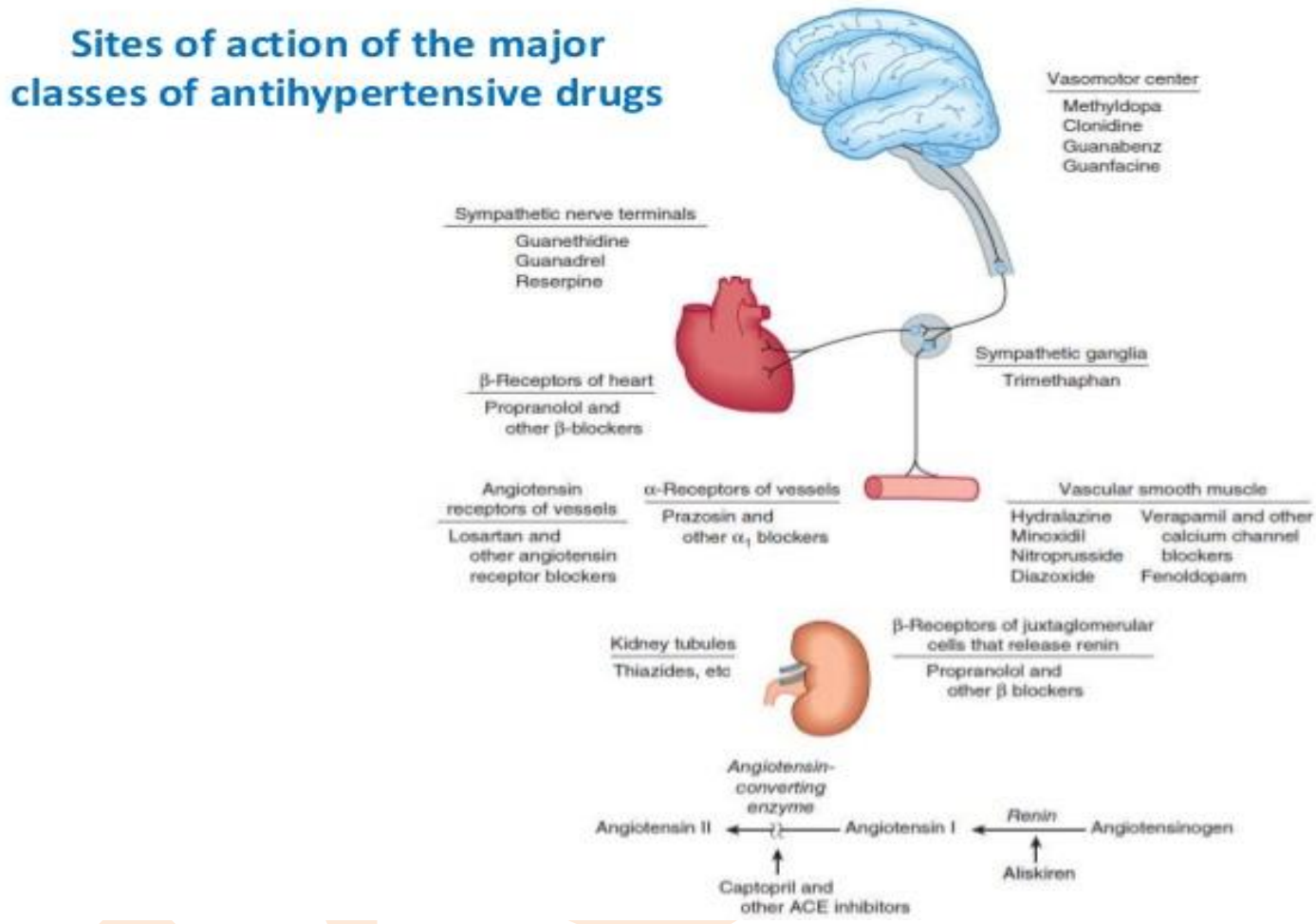
CLASS: 8

TOPIC: ANTI-HYPERTENSIVES

Hypertension: Blood pressure where blood exerts pressure against the walls of their blood vessels. It can lead to severe health complications and increase the risk of heart disease, stroke, and sometimes death.

This pressure depends on the resistance of the blood vessels and how hard the heart has to work.


CLASSIFICATION OF DRUGS
1.ACE INHIBITORS
Captopril,enalapril,lisinopril,perindopril,ramipril.
2.ANGIOTENSIN ANTAGONISTS
Losartan,irbesartan,candesartan
3.CALCIUM CHANNEL BLOCKERS
Verapamil,diltiazam,nifedipine,felodipine,amlodipine,lacidipine,
4.DIURETICS
Thiazide=hydrochlorothiazide,chlorthalidone.indapamide
High ceiling=furosemide
K+ sparing=spironolactone.amiloride,
5.ß - ADRENERGIC BLOCKERS
Propranolol,metaprolol,atenolol.
6.α+ß ADRENERGIC BLOCKERS
Labetalol,carvedilol.
7.α - ADRENERGIC BLOCKERS
prazosin.,terazosin,phentolamine
8.CENTRAL SYMPATHOLYTIC
Clonidine,methyldopa
9.VASODILATORS
Hydralazine,minoxidil sodium
7



Types of hypertension: There are two hypertension types. For 95 percent of people with high blood pressure, the cause of their hypertension is unknown — this is called essential, or primary, hypertension.

When a cause can be found, the condition is called secondary hypertension.

DRUGS:

PHARMACOGOLOGY-II- BP503T

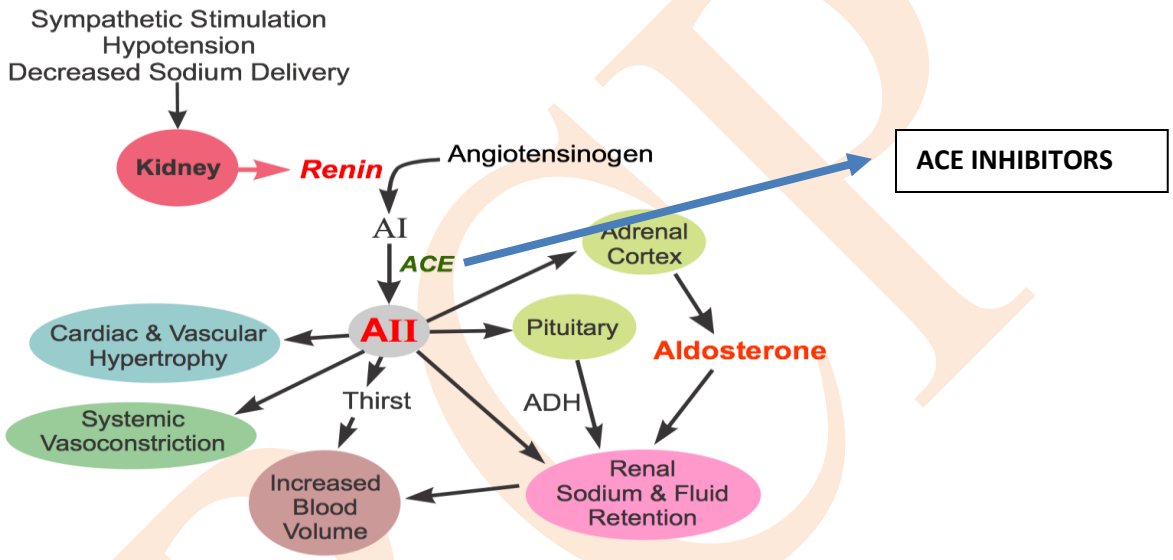
UNIT : 1(Cardiovascular system)

CLASS: 9

TOPIC: ACE INHIBITORS:

CAPTOPRIL

M.O.A:



Actions:

- ACEIs affect capacitance and resistance vessels, and reduce cardiac load as well as arterial pressure.
- The arterioles dilate and compliance of larger arteries is increased.
- Both systolic and diastolic BP fall.Hyptensive effect. increase plasma kinin levels and potentiate the hypotensive action of exogenously administered bradykinin.
- The arterioles dilate and compliance of larger arteries is increased. Both systolic and diastolic BP fall.

Clinical uses of angiotensin-converting enzyme inhibitors

• Hypertension.

• Cardiac failure.

• Following myocardial infarction (especially when there is ventricular dysfunction).

• In people at high risk of ischaemic heart disease.

• Diabetic nephropathy.

• Chronic renal insufficiency to prevent progression.

Kinetics:

ROA: ORAL

Metabolism: partly metabolised

Excretion: unchanged in urine

ADR:

1. Dry cough, possibly the result of accumulation of bradykinin.

2. Hypotension

3. Kinin accumulation may also underlie *angioedema* (painful swelling in tissues which can be life-threatening if it involves the airway).

Interaction:

Diuretics + ACE= Hypotension

Indomethacin- attenuate hypotensive effect

Hypertension, diabetic nephropathy, CHF, MI and Scleredoma crisis

Other drugs are: **Enalapril , Lisinopril, Trandolapril, Ramipril, Fosinopril, Imidapril, Perindopril, Benazepril.**

Angiotensin II receptor antagonists:

Losartan, **candesartan**, **valsartan** and **irbesartan** (sartans) are non-peptide, orally active AT1 receptor antagonists (ARBs).

Losartan:

It blocks all overt actions of A-II,

Losartan causes fall in BP in hypertensive
patients which lasts for 24 hours,

Pharmacologically, AT1 receptor antagonists differ from ACE inhibitors in the following ways:
• They do not interfere with degradation of bradykinin and other ACE substrates: no rise in level or potentiation of bradykinin occurs.

• They result in more complete inhibition of AT1 receptor activation, because alternative pathway of A-II generation and consequent AT1 receptor activation remain intact with ACE inhibitors.
• They result in indirect AT2 receptor activation. Due to blockade of AT1 receptor mediated feedback inhibition—more A-II is produced
which acts on AT2 receptors that remain unblocked. ACE inhibitors result in depression of both AT1 and AT2 activation.

M.A.O: Competitive antagonist

Selective for AT1 than AT2

It is a competitive antagonist and inverse agonist of A-II, 10,000 times more selective for AT1 than AT2 receptor;
Inhibits AT II vasoconstriction, central and peripheral sympathetic stimulation.

Kinetics:

ROA: Oral

Metabolism: First pass metabolism

Excretion: In urine through kidney

Uses:

Hypertension

Cardiac congestive heart failure

Myocardial infraction

Diabetic nephropathy

ADR: Losartan is well tolerated; has less side effects,
Hypotension, Angioedema

Headache, dizziness and weakness and upper g.i. side effects are mild and occasional. However, losartan has fetopathic potential like ACE inhibitors—not to be administered during pregnancy.

Other drugs are: **Telmisartan, Valsartan, Irbesartan, Candesartan**

Beta-blockers: Propranolol., Atenolol

The pharmacology and mechanism of antihypertensive action of β-blockers.
The hypotensive response to beta blockers develops over 1–3 weeks and is well sustained.

Mild anti-hypertensives

Hypotensive effect by lowering agonism.

Contraindication for beta blockers are cardiac pulmonary and peripheral vascular disease

Beta blockers are 1st choice of drugs.

Used for MI and effect on lipid profile.

Drugs with intrinsic sympathomimetic activity cause less reduction of HR and c.o. but lower vascular resistance by beta- agonism. The nonselective □□□blockers slightly reduce renal bloodflow and g.f.r., but this is minimal in the beta -selective ones and those with ISA.

Alpha + beta blockers:

Decreased total peripheral resistance and action faster than beta blockers.

ROA: IV for rapid ⬇ B.P.

Cardivilol: non selective Beta and selective alpha blocker vasodilation and antioxidant.

Drugs of aklpha + beta blockers Labetalol search ANS . It is a combined □□□β□blocker; reduces t.p.r. and acts faster than pure β□blockers.

Carvedilol This nonselective □+α selective □1 blocker produces vasodilatation and has additional antioxidant/ free radical scavenging properties.

Alpha-ADRENERGIC BLOCKERS
Prazosin
Prazosin (*See* ANS)
This prototype selective □1 antagonist dilates both resistance and capacitance vessels; It probably decreasescentral sympathetic tone also.

Terazosin, Doxazosin These are long-acting congeners of prazosin with similar properties and suitable for once daily dosing.

PHARMACOGOLOGY-II- BP503T

UNIT : 1(Cardiovascular system)

CLASS: 10

TOPIC: CENTRAL SYMPATHOLYTICS

Clonidine:

Clonidine is a partial agonist with high affinity and high intrinsic activity at α receptors, especially αA subtype in brainstem.
The major haemodynamic effects result from stimulation of αreceptors present mainly postjunctionally in medulla (vasomotor centre)→decrease sympathetic out flow causing fall in BP and bradycardia (also due to enhanced vagaltone).

Centrally acting adrenergic drugs

Clonidine

- Clonidine acts centrally as an α_2 agonist to produce inhibition of sympathetic vasomotor centers, decreasing sympathetic outflow to the periphery. This leads to reduced total peripheral resistance and decreased blood pressure. At present, it is occasionally used in combination with a diuretic.

Methyldopa

- It is an α_2 agonist that is converted to methylnorepinephrine centrally to diminish adrenergic outflow from the CNS. **It is mainly used for management of hypertension in pregnancy, where it has a record of safety.**

Kinetics of Clonidine:

ROA: ORAL

Metabolism: in liver

Excretion: unchanged in urine

ADR:

- Sedation, mental depression, disturbed sleep; dryness of mouth, nose and eyes .
- Impotence, salt and water retention. Alarming rise in BP, in excess of pretreatment level, with tachycardia, restlessness, anxiety.

Uses:

- risk of withdrawal hypertension
- development of tolerance.
- At present, it is occasionally used in combination with a diuretic.

Methyldopa:

It is the α-methyl analogue of dopa, the precursor of dopamine (DA) and NA.
M.O.A: methyldopa acts on central α2 receptors to decrease efferent sympathetic activity
Actions:

- methyldopa decreases t.p.r. more than HR or c.o.
- In large doses, methyldopa inhibits the enzyme dopa decarboxylase in brain and periphery and reduces NA synthesis and forms the *false transmitter*.
- Methyldopa is a moderate efficacy antihypertensive.

Kinetics:

- ROA: oral
- Metabolism: partly metabolised in liver
- Excretion: Partly excreted through urine

ADR:

- Sedation, lethargy and reduced mental capacity.
- Cognitive impairment may develop.
- Dryness of mouth,
- nasal stuffiness, headache, fluid retention, weight gain, impotence.
- Postural hypotension

USES:

- Methyldopa was a widely used antihypertensive, especially in combination with a diuretic.
- it is infrequently used now, except to treat hypertension during pregnancy.

PHARMACOGOLOGY-II- BP503T

UNIT : 1(Cardiovascualar system)

CLASS: 10

TOPIC: VASODILATORS

Hydralazine/Dihydralazine:

M.O.A: involve generation of NO (nitric oxide) and stimulation of cGMP.

Actions:

- It is a directly acting arteriolar vasodilator with little action on venous capacitance vessels;
- reduces Total peripheral resistance (t.p.r)
- It causes greater reduction of diastolic than systolic BP.

Kinetics:

ROA: Oral

Metabolism: first pass metabolism in liver by acetylation.

E: excreted in urine.

ADR:

Adverse effects are frequent and mainly due to vasodilatation.

- Facial flushing, conjunctival injection, throbbing headache, dizziness, palpitation, nasal stuffiness, fluid retention, edema, CHF.
- Postural hypotension is not prominent because of little action on veins: venous return and c.o. are not reduced.
- Paresthesias, tremor, muscle cramps, rarely peripheral neuritis.

Uses:

- Hydralazine can be used in patients with renal involvement.
- Contraindicated in older patients and in those with ischaemic heart disease.
- Preferred antihypertensives during pregnancy.

Minoxidil: It is a powerful vasodilator, the pattern of action resembling hydralazine. direct relaxation of arteriolar smooth muscle with little effect on venous capacitance.

Remain from running notes

Diazoxide This K+ channel opener dilator of arterioles was used in the past for rapid reduction of BP in hypertensive emergencies. It is administered by rapid i.v. injection.

Sodium nitroprusside

M.O.A: Endothelial cells, RBCs (and may be other cells) split nitroprusside to generate NO which relaxes vascular smooth muscle. The enzymes involved are different from those that produce NO from glyceryl trinitrate.

Actions:

It is a rapidly (within seconds) and consistently acting vasodilator; has brief duration of action (2–5 min)—vascular tone can be titrated with the rate of i.v. infusion. It relaxes both resistance and capacitance vessels: reduces t.p.r. as well as c.o.

Kinetics, ADR, Uses: from notes.