**Pharmacology of Cardiovascular System**

**Introduction**

The cardiovascular system is a collection of interacting structures designed to supplyoxygen and nutrients to living cells and to remove carbon dioxide and other wastes. Its major components are the:

**a.Blood :-**Is the vehicle for oxygen, nutrients and wastes.

**b.Blood Vessels :-**Are the conduits or channels through which the blood is moved.

**c.Heart** :-The heart is the pump that provides the primary motive force.

**d.Capillaries** :- The capillaries, minute (very small) vessels, provide exchange areas. For example, in the capillaries of the lungs, oxygen is added and carbon dioxide is removed from the blood.

**Congestive Heart Failure :- (CHF)**

 Congestive heart failuremay be defined as non-efficient pumping of the heart. Thisinefficiency in pumping the heart leadsto an increasein the size of theheart and anincrease in the heart rate. This increase in heart size and heart rate result because of the heart’s attempt to compensate for the poor efficiency in pumping blood to other parts of the body. Consequently, the kidneys improperly function.

Improperly functioning kidneys result in edema of the extremities due to improper excretion (removal) of sodium and waste products in the urine. In casesof acute CHF, Pulmonary edemawill be developed due to poor kidney function. Underlying causes of HF include arteriosclerotic heart disease,myocardial infarction, hypertensive heart disease, valvular heart disease,dilated cardiomyopathy, coronary disease and congenital heart disease.

**Symptoms of CHF :-**

* Dyspnea , orthopnea , fatigue , dependent edema .

**Treatment of Congestive Heart Failure:**

There are many categories used for treatment of **CHF**. Like:

1. **Inhibitors of rennin – angiotensin system: -**  this group of drugs acts by two ways those are:-
2. ***Angiotensin-converting enzyme inhibitors (ACE. Inhibitors):***
* ACE inhibitors block a specific enzyme (angiotensin converting enzyme) that converts **angiotensin I** to **angiotensin II**. Angiotensin II is one of the most potentvasoconstrictor in the body.
* ACE inhibitors also decrease the secretion of**aldosterone**resulting in decreased sodium and water retention. Consequently decrease edema.
* Agents included in this class include :-**Captopril** (Capoten®), **Enalapril**

(Vasotec®), **Lisinopril** (Prinivil®, Zestril®), and **Ramipril**(Altace®).

* **Pharmacokinetics**

All of the ACE inhibitors are orally bioavailable as a drug or prodrug. All but***captopril***and***lisinopril*** undergo hepatic conversion to active metabolites, so these agents may be preferred in patients withsevere hepatic impairment. ***Fosinopril*** is the only ACE inhibitor that is not eliminated primarily by the kidneys and does notrequire dose adjustment in patients with renal impairment. ***Enalapril***is the only drug in this class available intravenously.

* **Adverse effects**

Common side effects include dry cough, rash, fever, altered taste, hypotensionand hyperkalemia.



1. ***Angiotensin receptor blockers:***

This group acts by blocking the specific receptor of **angiotensin** ; the resultant effect will be seems to the previous group . **Angiotensin II** receptor blockers are used primarily for the treatment of **hypertension** where the patient is intolerant of **ACE inhibitor** therapy.

Example; **Losartan, Valsartan ,Telmisartan , Irbesartan , Azilsartan and Olmesartan .**

**2- β1-receptor blockers:**

Beta adrenergic blocking agents work by blocking:-

* Block β1-receptors on heart: Reduce heart rate and inotropic state.
* Block β1-receptors on kidneys: Reduce renin secretion.
* Block β1-receptors in CNS: Reduce sympathetic outflow leading to reducevasomotor tone.Example; **Carvedilol** (Coreg®) and **Metoprolol**(Lopressor®).
* **Therapeutic uses**

The primary therapeutic benefits of β-blockers are seen in hypertensive patients with concomitant heart disease, such as supraventriculartachyarrhythmia (for example, atrial fibrillation), previous myocardialinfarction, angina pectoris, and chronic heart failure.

* **Pharmacokinetics**

The β-blockers are orally active for the treatment of hypertension. Propranolol undergoes extensive and highly variable first-passmetabolism. Oral β-blockers may take several weeks to develop theirfull effects. Esmolol, metoprolol, and propranolol are available in intravenous formulations.

* **Adverse effects**

**1. Common effects:** The ß-blockers may cause bradycardia, hypo- tension, and CNS side effects such as fatigue, lethargy, and insomnia .

**2. Alterations in serum lipid patterns:**Noncardioselective ß-blockers may disturb lipid metabolism, decreasing high-density lipoprotein cholesterol and increasing triglycerides.

**3. Drug withdrawal**: Abrupt withdrawal may induce angina, myocardialinfarction, and even sudden death in patients with ischemic heart disease. Therefore, these drugs must be tapered over a few weeks in patients with hypertension and ischemic heart disease.

1. **Diuretics**

Diuretics are drugs that increase the volume of urine excreted. Mostdiuretic agents are inhibitors of renal ion transporters that decrease thereabsorption of Na+at different sites in the nephron. As a result, Na andother ions, such as Cl, enter the urine in greater than normal amountsalong with water, which is carried passively to maintain osmotic equilibrium.

The general uses of diuretics include the treatment of congestive heart failure, hypertension, glaucoma, ascites, toxemia of pregnancy, and diabetes insipid . In the case of CHF the diuretics relieve pulmonary congestion and peripheral edema. Example; **Furosemide, Bumetanide** and**Thiazide** diuretics (e.g. **Hydrochlorothiazide, Chlorthalidone**and **Chlorthiazide**).

* **Thiazide**

 Thiazide diuretics can be used as initial drug therapy for hypertension unless there are compelling reasons to choose another agent. Regardless of class, the initial mechanism of action of diuretics is based upon decreasing blood volume, which ultimately leads to decreased blood pressure. Low-dosediuretic therapy is safe, inexpensive, and effective in preventing stroke, myocardial infarction, and heart failure.

1. **Inotropic drugs:-**
2. **Digitalis Products**: (**Digoxin** and **Digitoxin**)

The cardiac glycosides are often called digitalis or digitalis glyco-sides, because most of the drugs come from the digitalis (foxglove)plant. They are a group of chemically similar compounds that canincrease the contractility of the heart muscle and, therefore, are usedin treating HF.

The digitalis glycosides have a low therapeutic index,with only a small difference between a therapeutic dose and dosesthat are toxic or even fatal. The most widely used agent is *digoxin*.*Digitoxin* is seldom used due to its considerabledurationof action.

* They have positive inotropic activity on the cardiac muscle (increase contractionforce).
* **Mechanism of action include**

Inhibition of **Na+/K+-ATPase** Pump leading toincrease intracellular Na+ in myocardium causing decreased expulsion of Ca+2 inmyocardium then tonically higher levels of intracellular Ca+2 lead to increase myocardial contractility.

* Digitalis products have very narrowmargin of safety. And therefore they mustuse under control.

**Pharmacokinetics:**

 Digoxin is available in oral and injectable formulations. It has a large volume of distribution, because it accumulates in muscle. The dosage is based on lean body weight. In acute situations such as symptomatic atrial fibrillation. Digoxin has a long half-life of 30 to 40 hours. It is mainly eliminated intact by the kidney, requiring dose adjustment in renal dysfunction.

**Toxicity of Cardiac Glycosides** Include**:**

• Gastrointestinal effects such asanorexia,nausea,vomiting and diarrhea.

• Cardiac effects such as bradycardia, heart block and arrhythmias .

• CNS effects such as headache, malaise, hallucinations, delirium and visual disturbances .

1. **β- adrenergic agonists:-**

Dobutamine the most common , β1- adrenergic receptors act by convert ATP to cyclic AMP this activate protein kinase lead to phosphorylate of Ca channel allow inflow of Ca.

1. **Phosphodiestrase inhibitors :-**

Amirinone and milrinone increase CAMP lead to increase Ca and cardiac contractility .

**5. Directvasodilators : - include**

Nitrates , Hydralazine , Isosorbidedinitrate , Sodium nitroprusside.

**Act by :-**

* Decrease in cardiac in preload and increase capacitance.
* Dilation of arteries lead to decrease in cardiac afterload and decrease resistance.

**6. Aldosterone antagonist ( Spironolactone )**

**Uses :-**

* Preventing salt retention
* Preventing myocardial hypertrophy
* Preventing hypokalemia
* Promotes potassium retention

**Adverse effect** :- gastric disturbances ( gastritis and peptic ulcer) , CNS effect , confusion ) , endocrine abnormalities such as decrease libido and menstrual irregularities.

**AntidysrhythmicAgents:**

 The rate and rhythm of heartbeats. ("Rate" refers to the number of times your heart beats per minute. "Rhythm" refers to the pattern of regular or irregular pulses produced as the heart beats).

The term antidysrhythmicdrugs referto the agents that suppress abnormal beats orrestore normal cardiac rhythm by depressing various properties of the myocardium (heart muscle). **This is a general mechanism of action for all these drugs.**

**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, Phenytoin, 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): Sodium Channel Blockers**

**Quinidine (Quiniglute®, Quinidex®).**

**-**Quinidine is an antiarrhythmic agent used in the treatment of atrial fibrillation and ventricular arrhythmias.

**-**From plant origin known by *Cinchona.*

**-** It blocks sodium channel so that there is an increase in threshold for excitability. It is well absorbed orally.

**-**The side effects associated with quinidine include:-hypersensitivity reactions, gastrointestinal (GI) disturbances (nausea, vomiting, and diarrhea) and a group of symptoms known as cinchonism. Some symptoms associated with cinchonism are tinnitus (ringing in the ears), vertigo (dizziness), and headaches.

**Procainamide (Pronestyl®).**

**-**Procainamide is used in thetreatment of atrial and ventricular arrhythmiasProcainamide is similar in chemical structure to procaine.

**-**It retains the quinidine like actions of procaine, but it is not rapidly hydrolyzed and its action persists long enough so that it is active even after oral as well as parenteral administration.

**-**Pharmacologically, procainamide is equivalent to quinidine. Procainamide may cause anorexia, nausea and vomiting, and drug hypersensitivity.

**Lidocaine (Xylocaine®).**

**-**Lidocaineis an agent that may be given intravenously in the treatment of ventricular arrhythmias. (Similar to quinidine).

**-**Large intravenous doses may produce convulsions, coma, and respiratory depression

**Phenytoin (Dilantin®).**

**-**Phenytoin is an agent that may be administered intravenously to reverse digitalis-induced arrhythmias.

**-**Rapid intravenous administration may cause bradycardia, hypotension,andcardiac arrest

**Class (II): Beta Adrenergic Blockers**

 Class II agents are ß-adrenergic antagonists, or ß-blockers. These drugs diminish depolarization and, thus, depress automaticity, prolong AV conduction, and decrease heart rate and contractility. Class II agents are useful in treating tachyarrhythmias caused by increased sympathetic activity. They are also used for atrial flutter and fibrillation and for AV nodal reentrant tachycardia.

Include:-

* **Propranolol** :use after cardial infraction , and in ventricular arrhythmias .
* **Metoprolol** : in cardiac arrhythmias
* **Esmolol**: is a very short acting B- blockers treatment acute arrhythmias

**Class (III): Potassium channel blockers**

Mechanism of action : block K channel so diminish outflow of K current during repolarization lead to prolong A.P.without effecting phase 0 .

**Include**:-

**Sotalol** : decrease sudden death following C.I, decrease ectopic beats and decrease oxygen demand treatment ventricular tachycardia.

**Amiodarone :**

Uses : treatment ventricular tachyarrhythmias

**Class (IV): Calcium channel blockers**

Mechanism of action :Ca channel blockers , decrease Ca in ward a current so decrease phase 4 spontaneous depolarization lead to slow conduction in tissue.

**Include : Verapamil and Diltiazem**

**Uses:**In treatment ventricular arrhythmias and in treatment hypertension and angina.

**Vasodilators*:***

A vasodilator is a drug that dilates blood vessels with a resultant increase in blood flow, these vasodilators act by producing relaxationof vascularsmooth muscle,primarilyin arteriesand arterioles.Thisresultsindecreasedperipheralresistanceand,therefore,bloodpressure. This type of drugs are used mainly for treatment of hypertension and angina pectoris.

* **GlycerylTrinitrate (Nitroglycerin)**.

**-**It is the most common smooth muscle relaxant vasodilator used in the treatment of acute angina pectoris.

**-**Side effects associated with this drug include headache, dizziness, and orthostatic hypotension.

**-**The vasodilation effect of the drug may be so sudden that circulating blood pools in vascular (vessel) beds. This may cause thepatient to become unconscious because of a lack of blood to the brain. Falling to the floor in a faint allows the immediate return of that blood flow to the brain and consciousness returns.

* **IsosorbideDinitrate (Isordil®, Sorbitrate®).**

**-**Isosorbidedinitrate is thought to be effective in the prophylactic treatment of angina pectoris, as well as the treatment of acute angina attacks.

**-**The side effects associated with this drug are headache and dizziness.

* **Hydralazine (Apresoline®) and Minoxidil (Loniten®).**
* Hydralazine and minoxidil are direct acting peripheral vasodilators used in the treatment of hypertension.

**-**Hydralazine may be prescribed in combination with an oral nitrate in the treatment of congestive heart failure.

**-**Minoxidil is a powerful arterial vasodilator, given orally for sever hypertension, duration of action is about 72 Hrs.

* **Prazacin.**

**-**Selective competitive blocker of α1 receptor.

**-**Decrease peripheral vascular resistance (relax the smooth muscles of arteriolesand veins) leading to decrease in arterial blood pressure.

**Antianginal Drugs:**

***Angina Pectoris****.*It is a condition manifestedby severe chest pain sometimes radiating down the left arm. The pain probably arises from ischemia (lack of oxygen) in the heartcaused by the increased demand for or decreased supply of oxygen. The strategy of treatment of this case depends on dilation of coronary blood vessels in order to relive the pain and reduce oxygen requirement of the cardiac muscle.

**The mainly used Antianginal drugs are:**

* **Ca+2 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.**

* **Nitrates and nitrites :**

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.

* **β1 receptor blockers:**

 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.**

**Blood Drugs**

1. **Platelet aggregation inhibitors :**

Platelet aggregation inhibitors work in different places of the clotting cascade and prevent platelet adhesion, therefore no clot formation.

1. **Aspirin ( Acetylsalicylic acid )**

 Aspirin is an important part of the treatment of those who have had a myocardial infarction (heart attack). Acetylsalicylic acid (aspirin) at low doses given intermittently decreases the synthesis of thromboxne A2without 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.

1. **Ticlopidine(Ticlid) and Clopidogrel (Plavix)** : are an antiplatelet drug in the thienopyridine family which is an adenosine diphosphate (ADP) receptor inhibitor..
2. **Abciximab(ReoPro)** : block glycoprotein receptor.
3. **Anticoagulants :**

Anticoagulants are chemical substances that prevent or reduce coagulation of blood, prolonging the clotting time.

1. **Thrombin inhibitors** : such as heparin bind with antithrombin III ( alpha – globulin ) lead to inhibit serine proteases and several clotting factor and factor Xa.
2. **Vitamin Kantagonists** :These oral anticoagulants are derived from coumarin, which is found in many plants. A prominent member of this class is warfarin (Coumadin). It takes at least 48 to 72 hours for the anticoagulant effect to develop. Warfarin decease vitamin K epoxide reductases lead to decrease vit. K regeneration from epoxide and diminish production of clotting factors and lack sufficient y- carboxyglutamyl side chain .
3. **Thrombolytic drugs :(**Thrombolysis) is the breakdown (lysis) of blood clots formed in blood vessels, using medication.
4. **Streptokinase** : one of the first agents activate a systemic fibrinolytic state lead to bleeding problems.
5. **Altepase :** act more locally on thrombotic fibrin to produce fibrinolysis .
* **Mechanism of action** : all act either directly or indirectly to convert plasminogen to plasmin .
* **Therapeutic uses** :Treatment of deep vein thrombosis and pulmonary embolism , treatment acut myocardial infraction and indissolve clots that result in strokes.
1. **Drugs used to treat bleeding :**
2. **Aminocaproic and tranexamie acid**

They are used in treatment of fibrinolytic state by inhibit plasminogen activation , the side effect is intravascular thrombosis.

1. **Protamine sulfate:**

This protein derived from fish sperm , is high in arginine content , it interacts with negative charge heparin forming a stable complex without anticoagulant activity .

1. **Vitamin K ( Phytonadione )**

Act by interfering with anticoagulant the response to vit. K is slow need about 24 hr.

1. **Agents used to treat anemia**
2. **Iron** :

Is store in intestinal mucosal cell as ferritin until needed by the body , iron deficiency result from a negative iron balance due to depletion of iron stores or inadequate intake .

1. **Folic acid** :

The primary use of folic acid in treating state that arise from in adequate level of the vitamins.

Folate deficiency may causeby :-

1. Increased deficiency in pregnancy .
2. Poor absorption .
3. Alcoholism .
4. Treatment with drugs that are dihydrofolatereductase inhibitors e.g. ( methotrexate ) the deficiency cause megaloblastic anemia ( increase size of RBC ) lead to decrease synthesis purines and pyrimidines lead to inability of erthropoietic tissue to make DNA.
5. **Cyanocobalamin( Vit. B12 )**

Deficiencies of vit. B12 result from either low dietary level or poor absorption due to failure of gastric parietal cells to produce intrinsic factor ( GP).