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Pharmacokinetics Profile Evaluation of Newly Discovered Cardiovascular Drugs

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ABSTRACT

Cardiovascular diseases are described as the diseases of the heart and blood vessel. Diseases associated with coronary arteries like angina and myocardial infarction as well as hypertensive, rheumatic heart disease, cardiomyopathy, abnormal heart rhythms etc. So, the cardiovascular drugs are mandatory to treat medical conditions associated with the heart. In India, deaths from CVD are increased due to high use of tobacco, unhealthy diet and obesity. So many drugs are invented in the past to treat the diseases associated with heart. Clinically drugs are used having different pharmacokinetic and pharmacodynamics profile. Different classes of drugs also show different mechanism of action based on the underlying causes. This review mainly gives the insight details of pharmacokinetic profile of various newly launched drugs along with the mechanism of drug actions.

Introduction

All the organs and tissues in the body require oxygen. This necessity is satisfied by the consistent progression of oxygen-conveying blood. The CVS is ensuring the progression of blood is consistent in the body to approach oxygen. Without an appropriately working CVS, our cells would be not able to perform the functions appropriately.Cardiovascular related diseases are the commom reason for the deaths worldwide.[1].Some important diseasesincludes:

Coronary heart disease which areassociated with the coronary vesselsare capable of supplying oxygen to the heartmuscle.Hypertension is another name for the elevated blood pressure. Blood pressure is defined as pressure generated in the blood vessels by the blood.. In most cases High Blood pressure does not show warnings or signs. When High Blood pressure isconsistent,itsmajorriskfactorsresultincoronaryarterydisease,stroke,heartfailure,arterial fibrillation, vision loss, chronic disease.

Hypertension is classified into two categories

I) Primary Hypertension: - It is the most common and rates high at about 90-95% cases. Primary hypertension is as a result of un-healthy lifestyle and genetic factors. The way people chose to live their lives is what increases the risks of hypertension [10]

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II) Secondary Hypertension: - It is less common compared to primary hypertension and rates 5-10% cases. Comparably it is also a type of High Blood Pressure which is as a result of identifiable causes [1]

Heart requires oxygen and nutrients to perform its function properly. So, for these purpose coronary arteries supply oxygenated blood and nutrients to heart to perform its function properly.

Blood vessels like arteries are elastic vessels that can expand and contract. But due to increase in age, elasticity becomes diminishing due to the adherence of plaque in the lining of the blood vessel. These plaques contain cholesterol (fatty material), waste from the cells, calcium. As these plaques are there so, they reduce the amount of space fromwhichbloodcanflow.Theseplaquescanalsodamagethearteriesandcanforbloodclot.

Sincetheheartisessentiallyalargemusclethatisconstantlycontractingandrelaxing, it requires its own blood supply to provide it with enough oxygen. This blood is supplied through a specific group of arteries known as the coronary arteries. When atherosclerosis occurs within the coronary arteries, it can lead to decreased blood supply to those areas of the heart that are affected. So less blood supply reduce the nutrient supply and lead to coronary heart disease as blood supply is restricted.

In **Angina,** coronary artery becomes blocked by the plaques and so heart does not get proper oxygen and nutrients. Pain is there because of the increase in the lactic acid – a waste product from heart muscles that are not getting enough oxygen. Lactic acid buildup is the same thing that causes pain in your arms or legs when exercising for a long period of time.

In **Heart attack,** heart muscles become completely died due to the complete blockage of arteriessothereisalack ofoxygenandnutrientsandunabletopumpbloodsopersonwilldie.

Arrythmia: Arrhythmia is related to the irregular rhythm of the heart[1.2, 3].

Pharmacokinetics of recently developed Cardio-vasculardrugs: Pharmacokinetic is important parameter to evaluate the activity of various drugs. The studies like absorption, distribution, metabolism and excretion of the drugs provides the complete profileof the various drugs. The pharmacokinetic as well as pharmacodynamics profile of various drugs are

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Nebivolol:

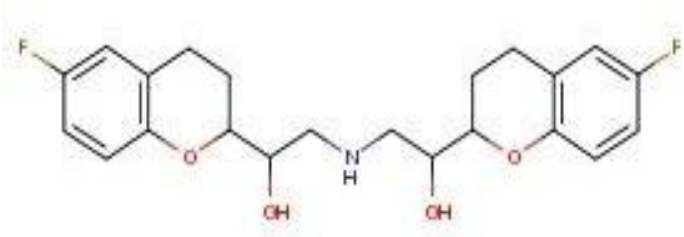

Figure 4: Structure of Nebivolol

Company: Allergan pharmaceuticals

Dosage form: Tablet

Dose strength: 2.5mg, 5mg, 10mg, 20mg

Interactions: Nebivolol show toxic interaction with some drugs like artemether or humefantrine.As these drugs is metabolized by hepatic enzyme CYP2D6

In pregnancy: Clinical studies not available and preclinical studies shows the risk factor

Pharmacology: Nabivolol consist of racemic mixture where one act on beta adrenergic receptors and second helps as cardiac stimulator. Nabivolol also proves to be more potent antihypertensive agents as compares to the other beta blockers like pindolol, atenolol and propranolol. Studies also provides the details about the effect of nabivolol for decreasing the systolic as well as diastolic blood pressures

Absorption: Nebivolol is taken as oral solution. The alteration in the kinetic profile of nabivolol is not observed by taking the food along or the presence of food.

Distribution: 20 mg of drug nabivolol shows the volume of distribution of 10,5L.

Metabolism: Nabivolol undergoes glucuronidation and CYP2D6 mediated hydroxylation for metabolism.

Excretion: 38% urine, 44% feces, <1% drug remain unchanged [4].

Mechanism of action: Nabivolol act as angonist for Beta 1 adrenergic receptor So it antagonize the action of epinephrine on heart. Epinephrine is one of the signaling molecule sympathetic

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nervous system which provides action on beta 1 adrenergic receptor and lead to increase in heart rate. Nabivolol as an antagonist block the receptor and causes decrease in heart rate as well as inhibit the production ofrenin in kidney which cause the constrictions in the blood vessels. Some studies also reported that administration of high dose of nabivolol also act on beta 2 receptors as well[5].

Tafamidis

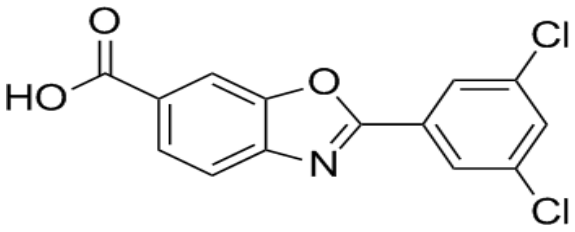

Figure 5: Structure of Tafamidis

Company: Pfizer pharmaceuticals

Dosage form: Capsule

Dose strength: 20 mg 4 times a day

Interactions: Tafamidismeglumine will elevate the action of alpelisib. Coadministration of alpelisib

In pregnancy: Sufficient data is not available to evaluate the effect of tefamidemeglumine in pregnant women. Moreover no any risk factor associated with this drug like birth defect, miscarriage or adverse fatal outcomes has been reported or identified,

Pharmacology:

Tafamidisis orally acrtive non NSAIDs drug. Tafamidis is a novel specific transthyretin (TTR) stabilizer assumes a tetramer configuration [6].

2.2.1 Pharmacokinetics of Tafamidis:

Absorption: Tafamideis available in tablets and capsules form of 20mg xoncentration and capable of achieving the peak plasma concentration within 2 hours

Distribution: Volume of distributionofdtug is found to be 18.5 L and drug approximately 99% bound to plasma.

Metabolism: Drug mainly undergo glucuronidation for metabolism

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Excretion: Half-life of tafamidis drug is 49 hourand oral clearance is 0.263 L/hr. The tafamidis is majorly excreted in Feces and urine.

Mechanismofaction: Tafamidis act as transthyretinstablizersso it binds to transthyretin protein and stabilizes it. [7]

Rivaroxaban

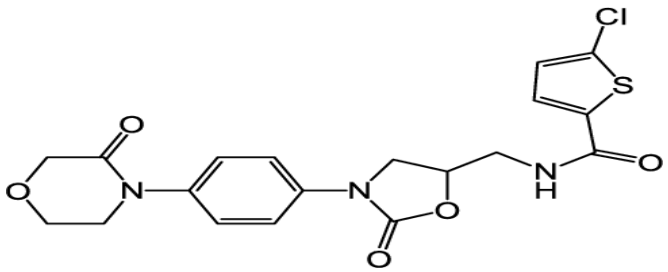

Figure: Structure of Rivaroxaban

Company: Janssen pharmaceuticals

Dosage form: Tablet (film coated)

Dose strength: 2.5mg, 10mg, 15mg, 20mg

Interaction: Betrixaban, Mifepristone, omacetaxine, Vorapaxar are the drugs whose toxicity increases by anticoagulation.

In pregnancy: Drug show interaction during pregnancy and can cause the excessive bleeding

Pharmacology: The Rivaroxaban shows anticoagulant action by inhibiting the factor Xa. Rivaroxaban is available as 10 mg tablets so it is orally active drug and till date no antidote for this drug is available[8. 9]

Pharmacokinetics parameters of Rivaroxaban:

Absorption: Rivaroxaban is capable of achieving the maximu plasma concentrationat a rapid rate of 2-4 hour with a single dose (1.25–80 mg) as well as on taking several doses.

Distribution: V_{SS} ~ 50 L (0.62l/kg), Low tissue penetration

Metabolism: 90% drug is unchanged in C_p, 50% drug is metabolized by liver by CYP3A4 (18%), CYP2J2 14%

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Excretion: In feces 28% of dose, 21% metabolites and 7% unchanged drug.

Mechanism of action: The mechanism of rivaroxaban is inhibition of clotting factor Xa. Factor Xa is primarily responsible for activation of fibrin from fibrinogen for the formation of mesh like structure at the area of injury. In the pathway of clotting formation activation of factor Xa primarily convert prothrombin into thrombin and thrombin then lead to activation of fibrin from fibrinogen. Therefore rivaroxaban act as anticoagulant but the action is irreversible [10].

Entresto (sacubitril andvalsartan):

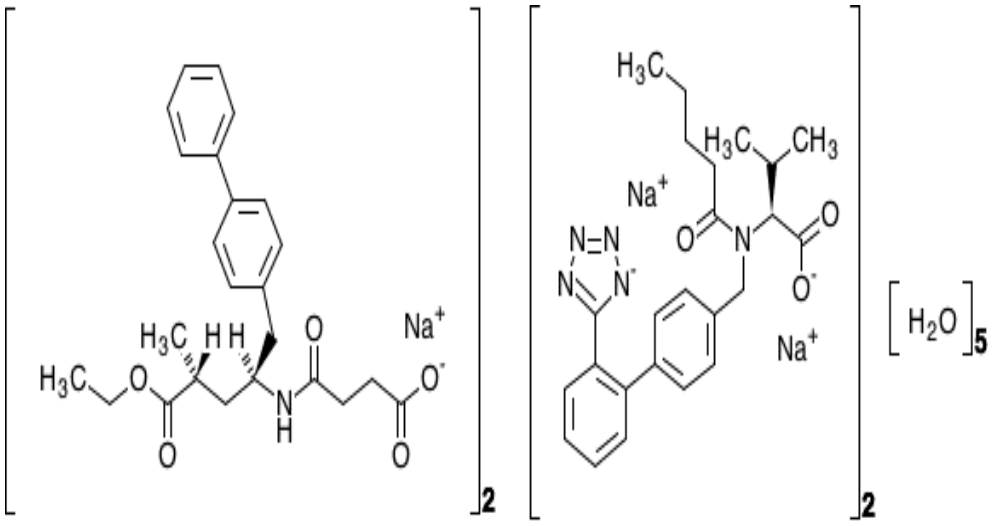

Figure: Chemical Structure of entresto

Company Name: Novartis

Dosage form: Tablet (film coated)

Dose strength: 24/26mg, 49/51mg, 97/103mg

Interactions: Drug is contraindicated with certain drugs those impaired renal functions

Pregnancy: Entresto is contraindicated during pregnancy as it may cause severe damage like neonatal skull hypoplasia and renal failure to fetal [11].

Pharmacology ofEntresto: Entresto formed by the combination of sacubitril, a neprilysin inhibitor, and valsartan, an angiotensin II receptor blocker indicated**:**

Valsartan: Valsartan shows angiotensin II receptor blocker (ARB) activity, ARBs primarily binds to angiotensin receptor 1 (AT1) and shows anti-hypertensive action. Overall, valsartan's

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helps to maintain the high blood pressure, decrease the levrel of aldosterone levels, lowers activity of cardiac activity and increased elimination of sodium ion as it causes increase blood volume. [12]

Sacubitril: is a prodrug which shows neprilysin inhibitor and reduce cardiovascular risk factor[13].

2.4.1 Pharmacokinetics ofEntresto:

Absorption: Oral tablet of Entresto breakdown into two molecules i.esacubitril and valsartan. The maximum plasma concentration also show variation between two and estimated to be 0.5 hours for Sacubitril and 1.5 hours foe valsartan. More than 60% of Sacubitril is orally bioavailable in plasma. Moreover valsartan show increase in the bioavailability when given as Entresto tablet as compare to the other formulation. Clinical as well as preclinical studies that Entresto can be given along with or without food as there is no change in absorption of the drug.

Distribution: Plasma protein binding of bothSacubitril and valsartan is high around 94-97%. Sacubitril dissociated into LBQ657 which has limited capacity for crossing blood brain barriers, Volumes of distribution for valsartan is 75L and sacubitril is 103 L.

Metabolism of Entresto: Sacubitril in Entresto get dissociated into LBQ657 through esterases. LBQ657 that was formed will not converted into further metabolites. Valsartanisminimallymetabolized

Excretion: Both sacubitral and valsartan are excreted from urine and feces [14]

Mechanism ofaction:ENTRESTO contains a neprilysin inhibitor, sacubitril, and an angiotensin receptor blocker, valsartan. ENTRESTO restrains neprilysin by means of LBQ657, the dynamic metabolite of the prodrug sacubitril, and obstructs the angiotensin II type-1 (AT1) receptor by means of valsartan. The cardiovascular and renal impacts of ENTRESTO in cardiovascular breakdown patients are ascribed to the expanded degrees of peptides that are debased by neprilysin, for example, natriuretic peptides, by LBQ657, and the concurrent hindrance of the impacts of angiotensin II by valsartan. Valsartan hinders the impacts of angiotensin II by specifically obstructing the AT1 receptor, and furthermore restrains angiotensin II-subordinate aldosterone

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discharge.[12]

Selexipag

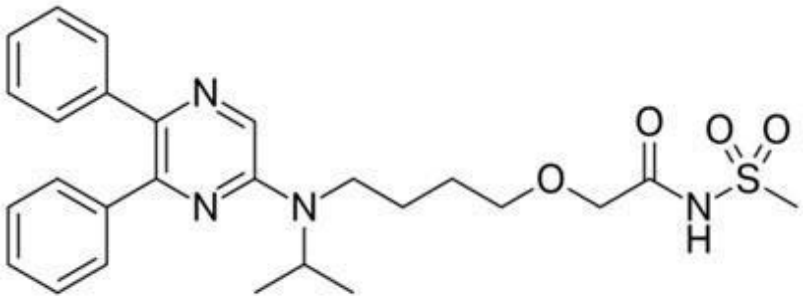

Figure: Structure of Selexipag

Company name: Actelion Pharmaceuticals

Dosage form: Tablet

Dosage strength: Selexipeg comes in different packaging of 200mcg, 400mcg, 600mcg,800mcg, 1000mcg, 1200mcg, 1400mcg and 1600mcg dose

Interaction: Gemfibrozil will increase the level of selexipag by decreasing metabolism. The drug is contraindicatedwith the drugs which are strong inhibitors of enzyme CYP2C8

Pregnancy: The studies of Selexipag on pregnant women are not available.

Pharmacology: Selexipag was initially invented for the treatment of hypertension and approved by United States FDA on December 22, 2015. The administration of selexipeg leads to reduce progression of disease as wekk as reduceriskofhospitalization.[15]

Pharmacokinetics ofSelexipag:

Absorption: Selexipag and its metabolite obtained the peak plasma concentration within 1-3 hours. Studies show that presence of food impaired the absorption of selexipag and lead to delay in achieving peak plasma concentration.

Distribution: drug id 99% plasma protein bound.

Metabolism: Selexipag dissociate into active metabolites by hydrolysis through carboxylesterases-1 enzymes**.**

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Excretion: Selexipag shows half-life of 0.8-2.5 hours and mostly excreted in feces. Selexipag shows no excretion through urine [16]

Mechanism ofaction:

Selexipag shows agonistic action on prostacyclin receptor agonist. Pulmonary hypertension occurs due to decrease the level of prostacyclinandprostacyclinsynthase in the respiratory lung. Prostacyclin is potent vasodilator and anti-inflammatory action so that's why the treatment of prostacyclin agonist is important aspect. Selexipag as well as its active metabolites shows activity for cardio protection.[17]

-Conclusion:

Cardiovascular diseases are the most common reasons of morbidity worldwide. so many drug discoveriesundergoforthetreatmentofdifferenttypesofcardiovasculardiseases.Sothemain purpose of this review to compile the details about the routes of drug administration , dose profile and complete pharmacokinetic data for recently launched drugs for cardiovascular diseaseThisreviewwillprovidethecompleteinformationaboutthedrugswhichwasrecently launchedforthetreatmentofvariouscardiovasculardiseasesaftertheconductofclinicaltrials. Also, this review provides us about the advantages and effectiveness of the new drugs. Why there is a need of these drugs. Which parameters these drugs are different from olderdrugs.

Table 1: Summary of the drugs

Sr. No.	Drug	Dose	Mechanism
1.	Nebivolol	2.5-20 mg	Beta-1receptor antagonist
2.	Tafamidis	20-80 mg	Transthyretin stabilizer
3.	Rivaroxaban	2.5-20 mg	Anticoagulant

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4.	Entresto	24/26mg,49/51mg, 97/103mg	Angiotensin2receptor blocker andinhibits neprilysin endopeptidase
5.	Selexipag	200-1600 mcg	Pulmonaryarterial hypertension

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