BP501T. MEDICINAL CHEMISTRY – II (Theory)

UNIT- III Notes

Author Details

Dr. Sidhartha Sankar Kar
Assistant Professor
Department of Pharmaceutical Chemistry,
Institute of Pharmacy & Technology, Salipur, Cuttack, Odisha.

Course Content:

UNIT- III **10 Hours**

Study of the development of the following classes of drugs, Classification, mechanism of action, uses of drugs mentioned in the course, Structure activity relationship of selective class of drugs as specified in the course and synthesis of drugs superscripted (*)

Anti-arrhythmic Drugs:

Quinidine sulphate, Procainamide hydrochloride, Disopyramide phosphate*, Phenytoin sodium, Lidocaine hydrochloride, Tocainide hydrochloride, Mexiletine hydrochloride, Lorcainide hydrochloride, Amiodarone, Sotalol.

Anti-hyperlipidemic agents:

Clofibrate, Lovastatin, Cholesteramine and Cholestipol

Coagulant & Anticoagulants:

Menadione, Acetomenadione, Warfarin*, Anisindione, clopidogrel

Drugs used in Congestive Heart Failure:

Digoxin, Digitoxin, Nesiritide, Bosentan, Tezosentan.

ANTI-ARRHYTHMIC DRUGS

Introduction

Cardiac arrhythmias remain a major source of morbidity and mortality in developed countries. Cardiac arrhythmia is a disturbance in the conduction of impulse through the myocardial tissue. These cardiac arrhythmias may be caused from disorders in pacemaker function of the sinoatrial node thereby resulting into tachycardia, bradycardia, cardiac arrest, atrial flutter, atrial fibrillation and ventricular fibrillation. Hence, the antiarrhythmic agents are also termed as 'antidysrhythmic drugs' or 'antifibrillatory drugs'.

Antiarrythmic drugs (AADs) may be defined as the "drugs that are capable of reverting any irregular cardiac rhythm or rate to normal".

Development

During the last 20 years, our understanding of cardiac electrophysiology and fundamental arrhythmia mechanisms has increased significantly, resulting in the identification of new potential targets for mechanism-based antiarrhythmic therapy. However, antiarrhythmic drug development has remained slow, despite much effort given our limited understanding of what role various ionic currents play in arrhythmogenesis and how they are modified by arrhythmias. Multichannel blockade, atrial selectivity, and the reduction of the risk of adverse events have all constituted the main theme of modern atrial fibrillation (AF) drug development. The increasing appreciation of ventricular arrhythmias as a marker of underlying heart disease and, therefore, a potential drug target, led to the development of multiple new antiarrhythmic drugs in the late 1970's and early 1980's. Most currently available AADs have been derived from naturally available compounds (e.g., quinidine adapted from a compound from the bark of the cinchona tree) or were originally developed for other purposes (e.g., amiodarone and sotalol were initially developed for the treatment of angina). The multiple electrophysiological effects of each of these compounds make mechanism-based therapy difficult.

Classification

The anti-arrhythmic drugs are categorized according to the Vaughan-Williams (VW) classification system. The VW classification anti-arrhythmic drugs are divided into four main categories based on their dominant electrophysiological properties. Recently it is being updated to more subcategories. They are as follows:

Table 1. Updated classification of anti-arrhythmic drugs.

Class	Subclass	Examples
		HCN channel blockers
0	-	Ivabradine
		Voltage-gated Na^+ channel blockers
I	**1a**	Quinidine, ajmaline, disopyramide
	1b	Lidocaine, mexiletine, phenytoin sodium
	1c	Propafenone, flecainide
	1d	Ranolazine
		Autonomic inhibitors and activators
II	**IIa**	Nonselective β inhibitors: carvedilol, propranolol Selective β1-adrenergic receptor inhibitors: atenolol, esmolol, metoprolol
	IIb	Isoproterenol
	IIc	Atropine, anisodamine, scopolamine
	IId	Carbachol, pilocarpine, methacholine,
	IIe	Adenosine, aminophylline
		K^+ channel blockers and openers
III	**IIIa**	Nonselective K^+ channel blockers: Ambasilide, amiodarone, dronedarone Selective K^+ channel blockers: Dofetilide, sotalol, vernakalant, tedisamil
	IIIb	Nicorandil, pinacidil
	IIIc	BMS 914392
		Ca^{2+} handling modulators
IV	**IVa**	Nonselective Ca^{2+} channel blockers: Bepridil Selective Ca^{2+} channel blockers: Verapamil, diltiazem
	IVb	Intracellular Ca^{2+} channel blockers: Flecainide, propafenone
		Mechanosensitive channel blockers
V		*N*-(p-amylcinnamoyl)anthranilic acid
		Gap junction channel blockers
VI		Carbenoxolone
		Upstream target modulators
VII		Angiotensin-converting enzyme inhibitors: Captopril, enalapril, imidapril Angiotensin receptor blockers: Losartan, candesartan, telmisartan Omega-3 fatty acids: eicosapentaenoic acid, docosahexaenoic acid
		Statins: Atorvastatin, lovastatin

Quinidine sulphate

- Quinidine is a class 1a (voltage-gated Na^+ channel blockers) anti-arrhythmic drug.
- It is a member of a family of alkaloids found in Cinchona bark (*Cinchona officinalis* L.).
- It is the dextrorotatory diastereomer of quinine.
- Quinidine and quinine are structurally similarity, but differ in their effects on the cardiac muscles, with the effects of quinidine being much more pronounced.
- The structure contains two basic nitrogens, of which the quinuclidine nitrogen is stronger base (p*K*a = 10).
- Because of the basic character of quinidine, it is always used as water -soluble salt forms. These salts include quinidine sulfate, gluconate, and polygalacturonate.
- The gluconate salt is particularly suited for parenteral use because of its high water solubility and lower irritant potential.

Mechanism of action

- Quinidine is a membrane stabilizing agent. It interferes directly with depolarization of the cardiac membrane.
- Quinidine binds with the voltage-gated sodium channels and inhibits the sodium influx required for the initiation and conduction of impulses.
- This results in an increase of the threshold for excitation and decreased depolarization during phase 0 of the action potential.
- In addition, the effective refractory period (ERP), action potential duration (APD), and ERP/APD ratios are increased, resulting in decreased conduction velocity of nerve impulses in the myocardium.

Uses

Quinidine should be used only after alternative measures have been found to be inadequate.

- Quinidine is used to treat and prevent atrial fibrillation or flutter and ventricular arrhythmias.
- Quinidine is also used to treat short QT syndrome.
- Quinidine is an intra-erythrocytic schizonticide, used to treat malaria.

Procainamide hydrochloride

- Procainamide is a class 1a (voltage-gated Na^+ channel blockers) anti-arrhythmic drug.

- It is the amide bio- isostere of local anesthetic procaine.
- Because of its amide structure, procainamide is more resistant to both enzymatic and chemical hydrolysis. It is orally active.

Mechanism of action

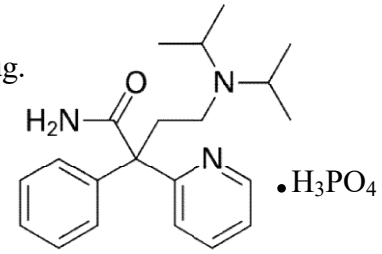
- Procainamide hydrochloride has mechanism of action similar to that of quinidine.
- Due to its charged and hydrophilic form, procainamide has its effect from the internal side, where it causes blockage of voltage-dependent, open channels.
- It reversibly binds to and blocks activated (open) voltage-gated sodium channels, thereby block the influx of sodium ions into the cell, which leads to an increase in threshold for excitation and inhibit depolarization during phase 0 of the action potential.
- The lasting action potential may also be due to blockage of outward K+ currents.
- The result is a decrease in automaticity, increase in refractory period and slowing of impulse conduction.

Uses

- Procainamide hydrochloride is used to suppress ventricular extrasystoles and paroxysmal ventricular tachycardia.
- It is also useful in the control and management of atrial fibrillation and premature atrial contractions.
- It has been also been used as a chromatography resin because it somewhat binds protein.

Disopyramide phosphate*

- Disopyramide phosphate is a Type 1a anti-arrhythmic drug.
- It is marketed as a racemic mixture



IUPAC name:

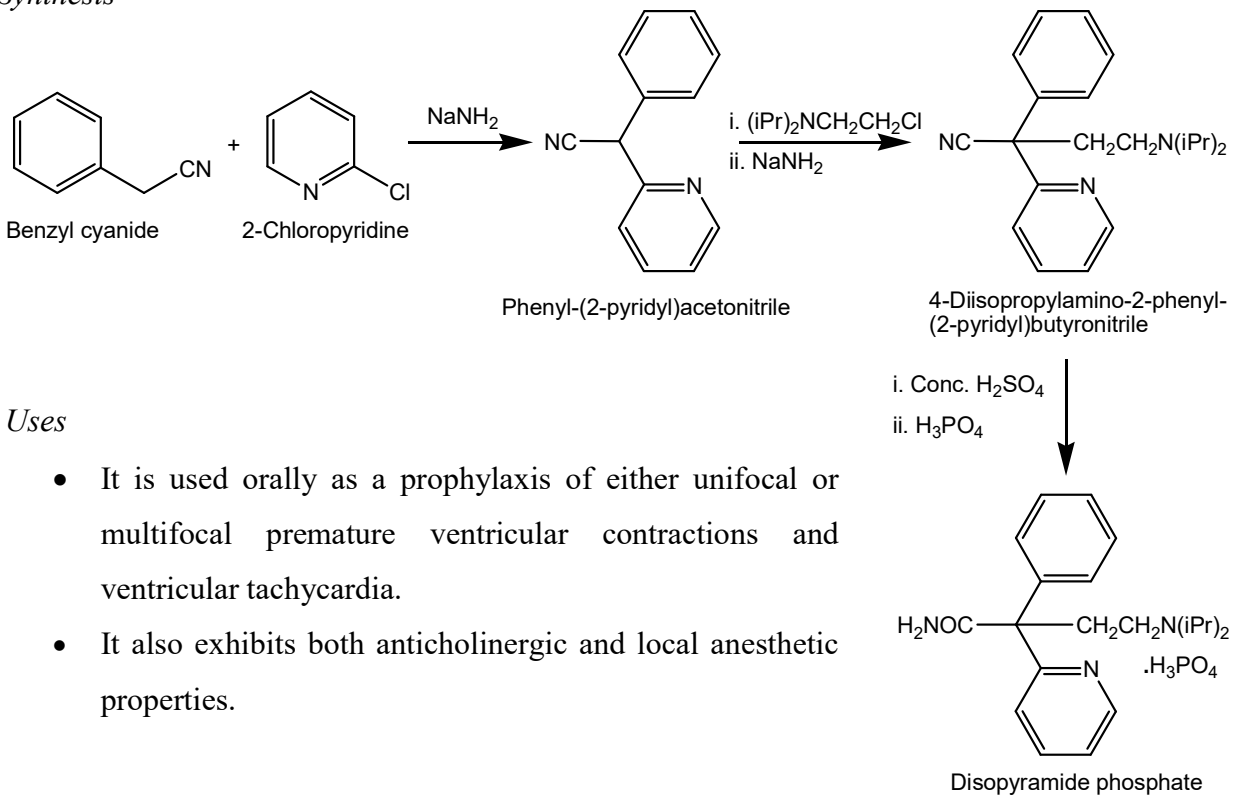
- 4-Diisopropylamino-2-phenyl-2-(2-pyridyl) butyramide phosphate
- 4-[di(propan-2-yl) amino]-2-phenyl-2-pyridin-2-ylbutanamide; phosphoric acid.

Mechanism of action

- Disopyramide phosphate has similar mechanism of action like procainamide and quinidine.

- It targets sodium channels to inhibit conduction.
- It decreases the rate of diastolic depolarization (phase 4) in cells with augmented automaticity, decreases the upstroke velocity (phase 0) and increases the action potential duration of normal cardiac cells, decreases the disparity in refractoriness between infracted and adjacent normally perfused myocardium.
- Disopyramide also has an anticholinergic effect on the heart which accounts for many adverse side effects.

Synthesis



Uses

- It is used orally as a prophylaxis of either unifocal or multifocal premature ventricular contractions and ventricular tachycardia.
- It also exhibits both anticholinergic and local anesthetic properties.

Phenytoin sodium

- Phenytoin sodium is the sodium salt form of phenytoin, a hydantoin derivate.
- It is a Type Ib anti-arrhythmic drug.

Mechanism of action

- Phenytoin sodium targets the voltage gated sodium channels in cardiac myocyte and purkinje fibre cell membranes.
- Phenytoin binds preferentially to the inactive form of the sodium channel.
- Because it takes time for the bound drug to dissociate from the inactive channel, there is a time dependent block of the channel.

- Since the fraction of inactive channels is increased by membrane depolarization as well as by repetitive firing, the binding to the inactive state by phenytoin sodium can produce voltage-dependent, use-dependent and time-dependent block of sodium-dependent action potentials.
- It reduces the maximum rate of depolarisation of the cardiac action potential and increases the effective refractory period.
- Therefore, it is particularly effective in inhibiting ventricular ectopy, especially in an ischaemic or damaged myocardium.

Uses

- Phenytoin sodium is a potential option for patients with refractory ventricular arrhythmia when other agents are contraindicated or unavailable.

Lidocaine hydrochloride

- Lignocaine is an amino amide class of drug also known as lidocaine.
- It is a class-1b antiarrhythmic drug.

Mechanism of action

- Lignocaine's cardiac effects, however, are distinctly different from those of procainamide or quinidine.
- It binds with equal affinity to both active and inactive sodium channels.
- It depresses diastolic depolarization and automaticity (depress Na+ influx during the diastole) in the Purkinje fibre network and increases the functional refractory period relative to action potential duration.
- It does not decrease the conduction velocity and increase membrane responsiveness to stimulation.

Uses

Lidocaine hydrochloride is administered intravenously in the acute management of

- Ventricular arrhythmias occurring during digitalis toxicity, cardiac surgery, or cardiac catheterization.
- Life-threatening arrhythmias, particularly those which are ventricular in origin, such as those which occur during acute myocardial infarction.

Tocainide hydrochloride

- Tocainide Hydrochloride is the hydrochloride salt form of tocainide.
- It is a primary amine analog of lidocaine exhibiting class 1b antiarrhythmic property.
- It is an α-methyl analogue structurally related to monoethylglycinexylide, the active metabolite of lidocaine.
- The α-methyl group slows the rate of metabolism and, thereby, to contribute to oral activity.

Mechanism of action

- Tocainide hydrochloride stabilizes the neuronal membrane by reversibly binding to and blocking open and inactivated voltage-gated sodium channels.
- This inhibits the inward sodium current required for the initiation and conduction of impulses and reduces the excitability of myocardial cells.
- This agent reduces the rate of rise and amplitude, and shortens the action-potential duration (APD) in both the Purkinje and muscle fibers.
- Tocainide also shortens the effective refractory period (ERP) of Purkinje fibers resulting in an increased the ERP/APD ratio.
- Overall these effects lead to the slowing of nerve impulses and stabilization of the heartbeat.

Uses

- It is used in ventricular arrhythmias, such as sustained ventricular tachycardia, that, in the judgment of the physician, are life-threatening.

Mexiletine hydrochloride

- Mexiletine hydrochloride is a class 1b anti-arrhythmic drug.
- It has a xylyl group like lidocaine in its structure.
- Chemically it is an ether, so it is comparatively resistant to hydrolysis during metabolism.

Mechanism of action

- Mexiletine hydrochloride works as a non-selective voltage-gated sodium channel blocker. Mexiletine, like lidocaine, inhibits the inward sodium current required for the initiation and conduction of impulses, thus reducing the rate of rise of the action potential, Phase 0.
- It achieves this reduced sodium current by inhibiting sodium channels.

- Mexiletine decreases the effective refractory period (ERP) in Purkinje fibers in the heart. The decrease in ERP is of lesser magnitude than the decrease in action potential duration (APD), which results in an increase in the ERP/APD ratio.
- It does not significantly affect resting membrane potential or sinus node automaticity, left ventricular function, systolic arterial blood pressure, atrioventricular (AV) conduction velocity, or QRS or QT intervals.

Uses

- It is used for the treatment of ventricular tachycardia and symptomatic premature ventricular beats, and prevention of ventricular fibrillation.
- It is used to treat muscle stiffness resulting from myotonic dystrophy (Steinert's disease) or nondystrophic myotonias such as myotonia congenita (Thomsen syndrome or Becker syndrome).

Lorcainide hydrochloride

- Lorcainide hydrochloride is a Class 1c antiarrhythmic agent.
- It is a member of acetamides.

Mechanism of action

- Lorcainide hydrochloride targets Voltage-gated Na^+ channel blockers in the inactivated state. This leads to marked block of open Na channels (decreases Phase 0).
- It has little effect on the repolarization phase and increases the PR and QRS interval.
- It decreases automaticity, conduction in depolarized cells.
- It decreases the rate of change of the depolarization phage of the action potential.

Uses

- It is used to help restore normal heart rhythm and conduction in patients with premature ventricular contractions, ventricular tachycardiac and Wolff-Parkinson-White syndrome.
- It is very effective particularly during chronic therapy perhaps due to its inherent high first-pass metabolism orally.

Amiodarone

- Amiodarone is a class IIIa antiarrhythmic drug.
- Chemically it is a benzofuran derivative.

- The molecular structure of amiodarone has some similarities with iodothyronines.

Mechanism of action

- Amiodarone is a nonselective K^+ channel blockers.
- It works primarily by blocking potassium rectifier currents that are responsible for the repolarization of the heart during phase 3 of the cardiac action potential.
- This potassium channel-blocking effect results in increased action potential duration and a prolonged effective refractory period in cardiac myocytes.
- Myocyte excitability is decreased, preventing reentry mechanisms and ectopic foci from perpetuating tachyarrhythmias.
- Electrocardiographic evidence of these effects is evident as prolongation of the QRS duration and QT interval.
- Unlike other class III agents, amiodarone also interferes with beta-adrenergic receptors, calcium channels, and sodium channels.

Uses

- Amiodarone is one of the most commonly used and prescribed antiarrhythmic drugs.
- It is frequently employed in the control and management of ventricular and supraventricular arrhythmias, and also in the treatment of angina pectoris.

Sotalol.

- Sotalol is a class IIIa antiarrhythmic drug.
- It has effects that are related to class II drugs.
- Chemically it is a sulfonamide that is N-phenylmethanesulfonamide.
- It contains a chiral centre and marketed as the racemic mixture.

Mechanism of action

- The levo enantiomer of satolol has both β-blocking (class II) and potassium channel blocking (class III) activities. The dextro enantiomer has class III properties.
- Sotalol is a nonselective beta-adrenergic receptor and competitive inhibitor of the rapid potassium channel potassium channel.
- In the heart, this agent inhibits chronotropic and inotropic effects thereby slowing the heart rate and decreasing myocardial contractility.

- This agent also reduces sinus rate, slows conduction in the atria and in the atrioventricular (AV) node and increases the functional refractory period of the AV node.

Uses

- Sotalol is used to treat life threatening ventricular arrhytmias and maintain normal sinus rhythm in patients with atrial fibrillation or flutter.
- Due to the risk of serious side effects, the FDA states that sotalol should generally be reserved for patients whose ventricular arrhythmias are life-threatening, or whose fibrillation/flutter cannot be resolved using simple methods.

ANTI-HYPERLIPIDEMIC AGENTS

Introduction

The major lipids found in the bloodstream are cholesterol, cholesterol esters, triglycerides, and phospholipids. An excess plasma concentration of one or more of these compounds is known as hyperlipidemia. This disease is usually chronic and requires continuous medication to control blood lipid levels. Hyperlipidemias are classified according to which types of lipids are elevated, that is hypercholesterolemia, hypertriglyceridemia or both in combined hyperlipidemia. Hyperlipoproteinemia has been strongly associated with atherosclerotic lesions and coronary heart disease (CHD).

Antihyperlipidemic agents promote reduction of lipid levels in the blood. Some antihyperlipidemic agents aim to lower the levels of low-density lipoprotein (LDL) cholesterol, some reduce triglyceride levels, and some help raise the high-density lipoprotein (HDL) cholesterol.

Classification of antihyperlipidemic agents

- Hydroxymethylglutaryl-CoA (HMGCoA) reductase inhibitors Ex. Statins (Atrovastatin, lovastatin, Metastatin, Pravastatin, Fluvastatin)
- Phenoxyisobutyric acid derivatives Ex. Fibrates (Clofibrates, Gemfibrozil)
- Pyridine derivatives Ex. Nicotinic acid, Nicotinamide
- Bile acid sequestrans Ex. Cholestyramine, Colestipol
- Cholesterol absorption inhibitors Ex. Ezetimibe
- LDL oxidation inhibitors Ex. Probucol
- Proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors Ex. Alirocumab

- Miscellaneous Antihyperlipidemic Agents Ex. β-Sitosterol, Dextrothyroxine

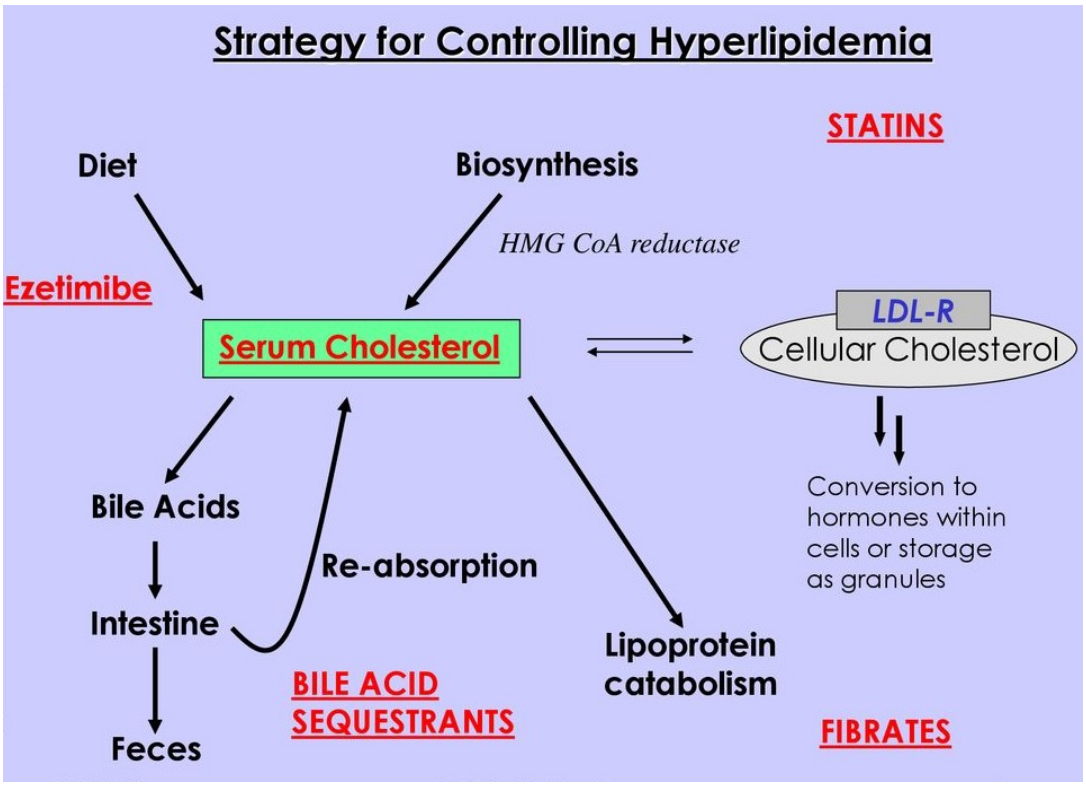


Figure 1. Mechanism of actions of antihyperlipidemic agents.

Clofibrate (CLOF)

- Clofibrate is an ester of phenoxyisobutyric acid (fibric acid).
- It is regarded as a broad spectrum lipid lowering drug.
- It is a prodrug, metabolized to chlorophenoxyisobutyric acid (CPIB) which is the active form of the drug.

Mechanism of action

- Clofibrate increases the activity of extrahepatic lipoprotein lipase (LL), thereby increasing lipoprotein triglyceride lipolysis.
- Chylomicrons are degraded, VLDLs (Very low density lipoprotein) are converted to LDLs, and LDLs are converted to HDL.
- This is accompanied by a slight increase in secretion of lipids into the bile and ultimately the intestine.
- Clofibrate also inhibits the synthesis and increases the clearance of apolipoprotein B, a carrier molecule for VLDL.

- Also, as a fibrate, clofibrate is an agonist of the PPAR-α receptor (peroxisome proliferator-activated receptor alpha) in muscle, liver, and other tissues.
- This agonism ultimately leads to modification in gene expression resulting in increased beta-oxidation, decreased triglyceride secretion, increased HDL, and increased lipoprotein lipase activity.

Uses

- It is used as an anticholesteremic agents or antilipemic agents.
- It is also used to treat xanthoma tuberosum and type III hyperlipidemia that doesn't respond adequately to diet.
- Clofibrate was discontinued in 2002 due to adverse effects.

Lovastatin

- Lovastatin is a fungal polyketide derived synthetically from a fermentation product of *Aspergillus terreus*.
- It is a prodrug.
- The inactive gamma-lactone closed ring form is hydrolysed *in vivo* to the active β-hydroxy acid open ring form.
- Lovastatin was the first specific inhibitor of HMG CoA reductase to receive approval for the treatment of hypercholesterolemia.

Mechanism of action

- Lovastatin is a potent competitive reversible inhibitors of HMG-CoA reductase.
- HMH-CoA reductase enzyme is required for mevalonate synthesis which an important building blocks in cholesterol biosynthesis.
- Lovastatin acts primarily in the liver, where decreased hepatic cholesterol concentrations stimulate the upregulation of hepatic low density lipoprotein (LDL) receptors which increase hepatic uptake of LDL.
- Lovastatin also inhibits hepatic synthesis of very low density lipoprotein (VLDL).
- The overall effect is a decrease in plasma LDL and VLDL and a significant reduction in the risk of development of CVD and all-cause mortality.

Uses

- Lovastatin is used to reduce the risk of myocardial infarction, unstable angina, and the need for coronary revascularization procedures in individuals without symptomatic cardiovascular disease
- Lovastatin is also used to slow the progression of coronary atherosclerosis in patients with coronary heart disease.

Cholesteramine

- Cholestyramine or colestyramine is a bile acid sequestrant.
- Cholesteramine is the chloride form a highly basic anion exchange resin.
- It is a styrene copolymer with divinylbenzene with quaternary ammonium groups.
- Cholestyramine resin is quite hydrophilic, but insoluble in water.

Mechanism of action

- Cholestyramine limits the reabsorption of bile acids in the gastrointestinal tract.
- Cholestyramine resin is a strong anion exchange resin, allowing it to exchange its chloride anions with anionic bile acids present in the gastrointestinal tract.
- Forms an insoluble complex resin matrix in the intestine which is excreted in the feces.
- This results in a partial removal of bile acids from the enterohepatic circulation by preventing their absorption.

Uses

- Cholestyramine is used to lower high levels of cholesterol in the blood, especially LDL.
- Cholestyramine powder is also used to treat itching caused by a blockage in the bile ducts of the gallbladder.

Cholestipol

- Colestipol is a bile acid sequestrant.
- It is an anion exchange resin.
- It is hydrophilic, but it is water-insoluble (99.75%).

Mechanism of action

- Colestipol is a water insoluble and high molecular weight polymer.
- It binds with bile acids to forms complex in the intestine.

- This complex cannot be reabsorbed due to its high molecular weight and low solubility and ultimately excreted in the feces.
- This increased fecal loss of bile acids due to colestipol interrupt the enterohepatic circulation of bile acids. Hence, cholesterol conversion to bile acids is enhanced.
- This results in an increased uptake of LDL and a decrease in serum/plasma beta lipoprotein or total and LDL cholesterol levels.

Uses

- Colestipol is indicated as adjunctive therapy to diet for the reduction of elevated serum total and low-density lipoprotein cholesterol (LDL-C) in patients with primary hypercholesterolemia who do not respond adequately to dietary changes.

COAGULANT & ANTICOAGULANTS

Blood must remain fluid within the vessels and yet clot quickly when exposed to subendothelial surfaces at sites of vascular injury. Under normal circumstances, a delicate balance between coagulation and fibrinolysis prevents both thrombosis and hemorrhage. Alteration of this balance in favor of coagulation results in thrombosis.

Blood Coagulation

It is a complex process of enzymatic reactions in which clotting factors activate other clotting factors in a fixed sequence until a clot is formed. It depends on the existence of a complex system of reactions involving plasma proteins, platelets, tissue factors and calcium ion. The coagulation process can be activated and proceed through one of two possible sequential pathways:

- Intrinsic system path: components present within the circulating blood,
- Extrinsic system: components present in the extravascular and intravascular compartment.

Cooperative integration of these two systems, along with circulating platelets, maintains vascular integrity and preserves hemostasis.

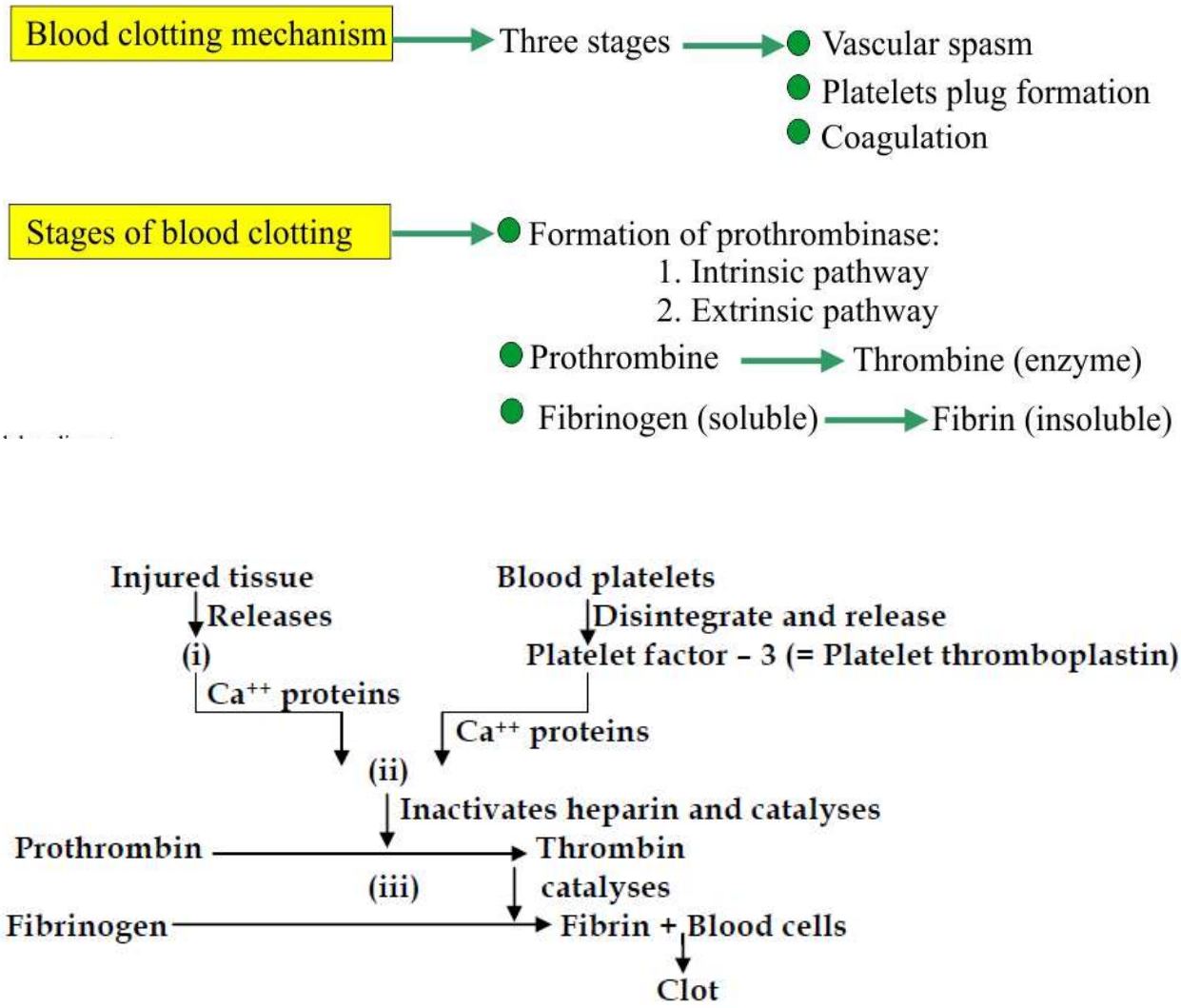


Figure 2. Stages and mechanism of blood clotting.

Bleeding disorders or hemorrhages like Haemophilia, Von willibrands result when the blood lacks certain clotting factors. A variety of pathological and toxicological condi tions can result in excessive bleeding from inadequate coagulation. Depending on the etiology and severity of the hemorrhagic episode, several possible blood coagulation inducers can be therapeutically employed.

Coagulants

Coagulants are substances which promote coagulation indicated in hemorrhagic states like Haemophilia,Von willibrands disease, etc.

Classification of anticoagulants

Vitamin K	**K1 (from plants fat-soluble):**	**Phytonadione (Phylloquinone)**
	K3 (synthetic)	
	—Fat-soluble:	Menadione, Acetomenaphthone
	—Water-soluble:	Menadione sod. Bisulfite, Menadione, sod. Diphosphate
Miscellaneous	Fibrinogen (human), Antihaemophilic factor, Desmopressin, Adrenochrome monosemicarbazone, Rutin, Ethamsylate	

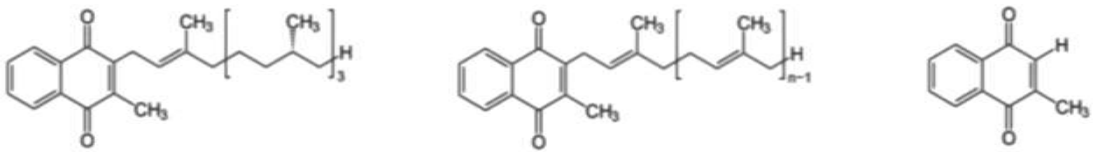
Menadione

- Menadione is a synthetic naphthoquinone (analog of 1,4-naphthoquinone).
- It is also called as vitamin K_3.
- It is a prothrombin activator.

Mechanism of action

- Menadione (Vitamin K_3) is a fat-soluble vitamin precursor that is converted into active menaquinone (vitamin K_2) after alkylation in the liver.
- It acts as a cofactor in the synthesis of coagulation proteins; prothrombin, factors VII, IX, and X by liver.
- Vitamin K helps in gama-carboxylation of these clotting factors where their descarboxy-forms get converted in to active forms.
- Now this active form of clotting factors have the capacity to bind with Ca^{2+} and to get bound to the phospholipid surfaces which are essential properties for participation in the coagulation process.

Vitamin K1 (Phylloquinone) Vitamin K2 (Menaquinone) Vitamin K3 (Menadione)



Uses

- It is used in the treatment of hypoprothrombinemia.
- It may also play a role in normal bone calcification.

Acetomenadione

- Acetomenadione is a member of naphthalenes.
- It is a synthetic vitamin.
- It is also known as davitamon-K or acetomenaphthone.
- Acetomenaphthone is an extremely weak basic

Mechanism of action

Refer the mechanism of action of menadione.

Uses

Acetomenadione is used for the treatment, control, prevention, & improvement of the following diseases, conditions and symptoms:

- Coagulation disorders due to vitamin K deficiency
- Anticoagulant-induced prothrombin deficiency

Anticoagulants

Drugs that interfere with blood coagulation (anticoagulants) are known as anticoagulants. They are the mainstay of cardiovascular therapy. Anticoagulants eliminate or reduce the risk of blood clots. They're often called blood thinners, but these medications don't really thin your blood. Instead, they help prevent or break up dangerous blood clots that form in your blood vessels or heart.

Classification

1. Used *in vivo*
    a. Parenteral anticoagulants
        i. Indirect thrombin inhibitors Ex. Heparin, Danaparoid, Fondaparinux
        ii. Direct thrombin inhibitors Ex. Lepirudin, Bivalirudin, Argatroban
    b. Oral anticoagulants
        i. Coumarin derivatives Ex. Warfarin, Bishydroxycoumarin, Acenocoumarol

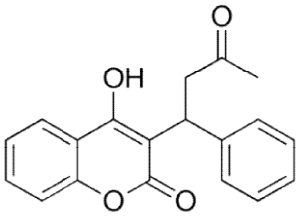
ii. Indanedione derivatives Ex. Phenindione
iii. Direct factor Xa inhibitors Ex. Rivaroxaban
iv. Oral direct thrombin inhibitors Ex. Dabigatran,

2. Used *in vitro*

Heparin

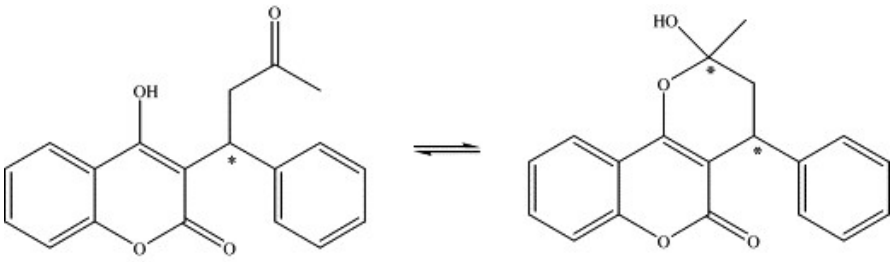
Calcium complexing agents

i. Oxalate compounds Ex. Calcium oxalate
ii. Citrate compounds Ex. Sodium citrate



Warfarin

- Warfarin is a synthetic anticoagulant.
- *IUPAC Name:* 4-hydroxy-3-(3-oxo-1-phenylbutyl)chromen-2-one.
- The name *warfarin* came from its discovery at the, *WARF* (Wisconsin Alumni Research Foundation) and the ending *-arin*, indicates its link with coumarin.
- Warfarin exists in tautomeric form.
- Hemiketal must tautomerise to the 4-hydroxy form in order for warfarin to be active.
- Warfarin contains a stereocenter and consists of two enantiomers. This is a racemate.
- Anticoagulant activity of S-warfarin is 2–5 times more than the R-isomer.



Open chain Cyclic hemiketal

Mechanism of action

- Warfarin acts by antagonizing vitamin K and reduction of the factors involved directly or indirectly in blood clotting.
- Warfarin inhibits vitamin K reductase enzyme, which results in decrease amount of reduced form of vitamin K.
- Reduction in vitamin K (reduced) lowers down the glutamate residues carboxylation in the N-terminal regions of coagulant proteins.

- This inhibits the synthesis of vitamin K-dependent coagulation factors (factors II, VII, IX, and X) and anticoagulant proteins (regulatory factors) C and S by the liver.
- Decrease in the coagulation factors causes lowering in the prothrombin levels.
- Reduce prothrombin affects production of thrombin and fibrin bound thrombin,which ultimately reduces blood clotting.

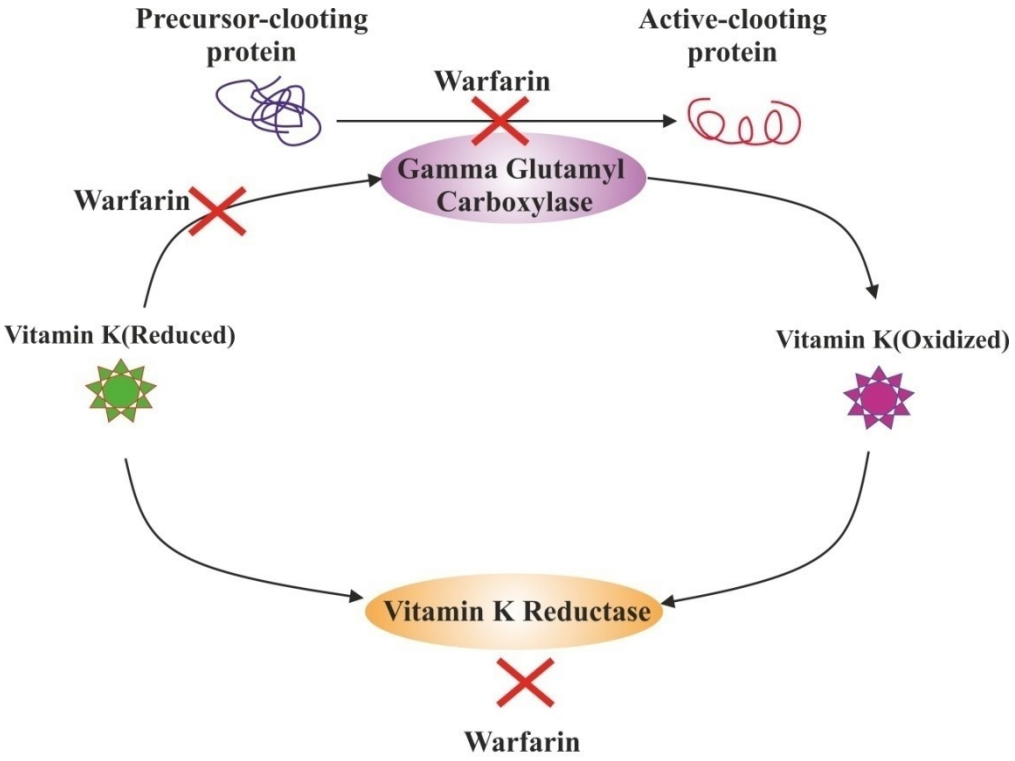
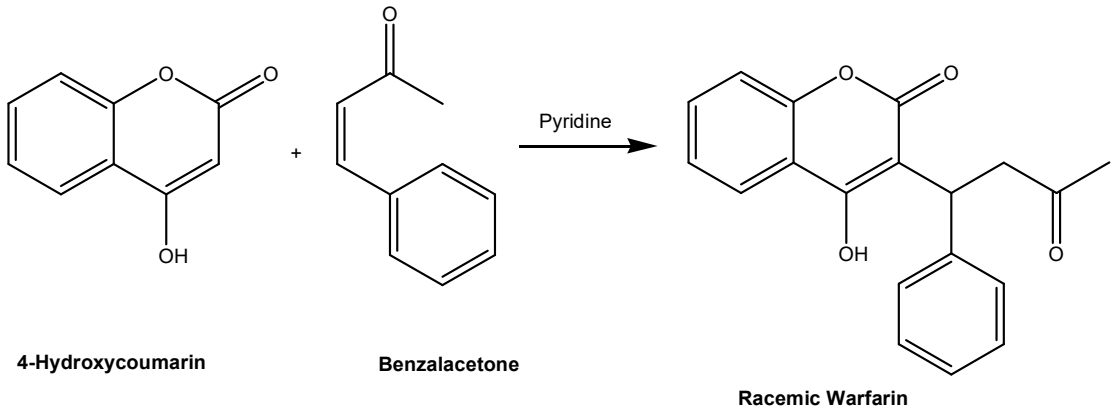


Figure 2. Mechanism of action of warfarin.

Synthesis



Base/acid catalysed Michael condensation reaction of 4-hydroxycoumarin with benzalacetone. Pyridine is usually used as the catalyst for this reaction to afford racemic warfarin.

Uses

- Prophylaxis and treatment of venous thromboembolism and related pulmonary embolism.
- Prophylaxis and treatment of thromboembolism associated with atrial fibrillation.
- Prophylaxis and treatment of thromboembolism associated with cardiac valve replacement.
- Used as adjunct therapy to reduce mortality, recurrent myocardial infarction, and thromboembolic events post myocardial infarction.
- Secondary prevention of stroke and transient ischemic attacks in patients with rheumatic mitral valve disease but without atrial fibrillation.

Anisindione

- Anisindione is a synthetic indanedione anticoagulant.

Mechanism of action

- Anisindione inhibits the vitamin K–mediated gamma-carboxylation of precursor proteins.
- This prevents the formation of active procoagulation factors II, VII, IX, and X, as well as the anticoagulant proteins C and S.
- The consequential effects of this inhibition include a reduced activity of these clotting factors and prolonged blood clotting time.
- Anisindione has no direct thrombolytic effect and does not reverse ischemic tissue damage, although it may limit extension of existing thrombi and prevent secondary thromboembolic complications.

Uses

- For the prophylaxis and treatment of venous thrombosis and its extension, the treatment of atrial fibrillation with embolization, the prophylaxis and treatment of pulmonary embolism, and as an adjunct in the treatment of coronary occlusion.
- It is prescribed only if coumarin-type anticoagulants cannot be taken.

Clopidogrel

- Clopidogrel is a prodrug of the thienopyridine family.

Mechanism of action

- Clopidogrel is a prodrug and its thiol metabolite is a platelet inhibitor.

- Clopidogrel is metabolized to its active form in two steps in the liver by cytochrome P450 enzymes.
- The active thiol metabolite irreversibly inhibits the $P2Y_{12}$ subtype of ADP (adenosine diphosphate) receptor on the platelet surface.
- This leads to disruption of resulting in platelet aggregation.

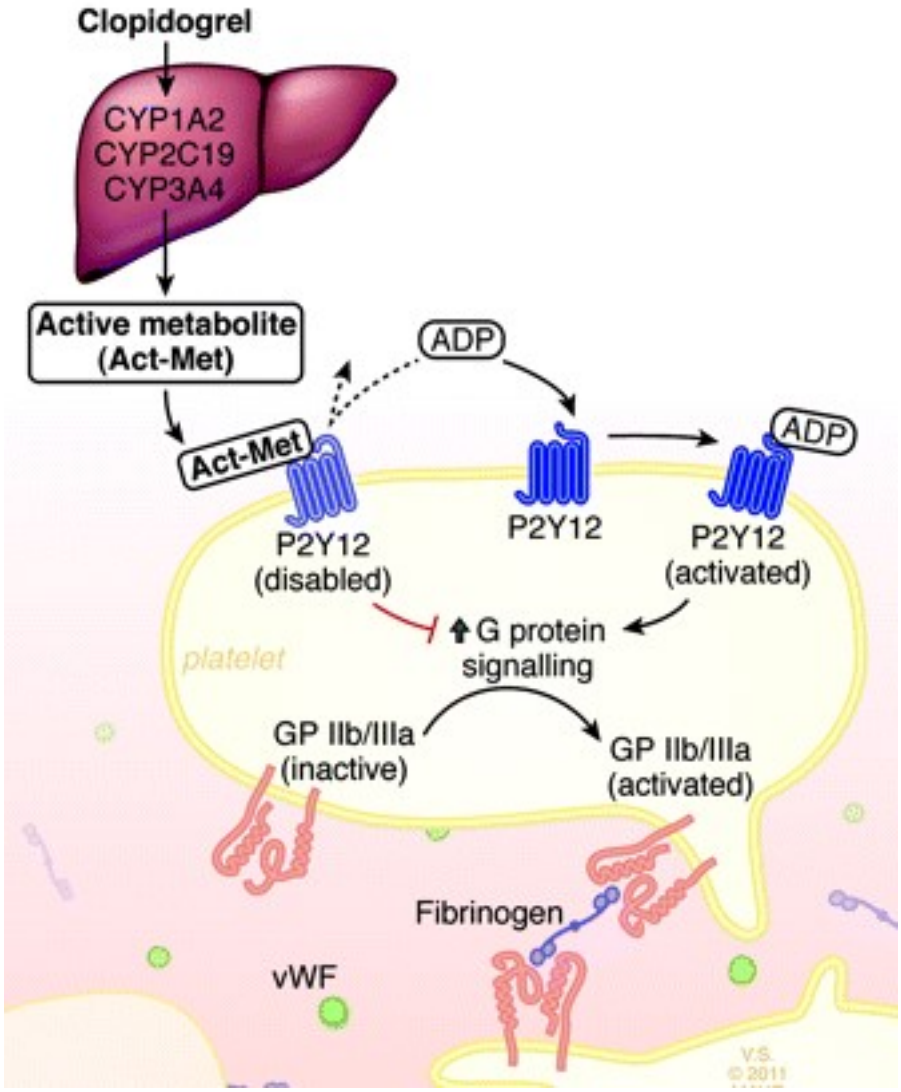


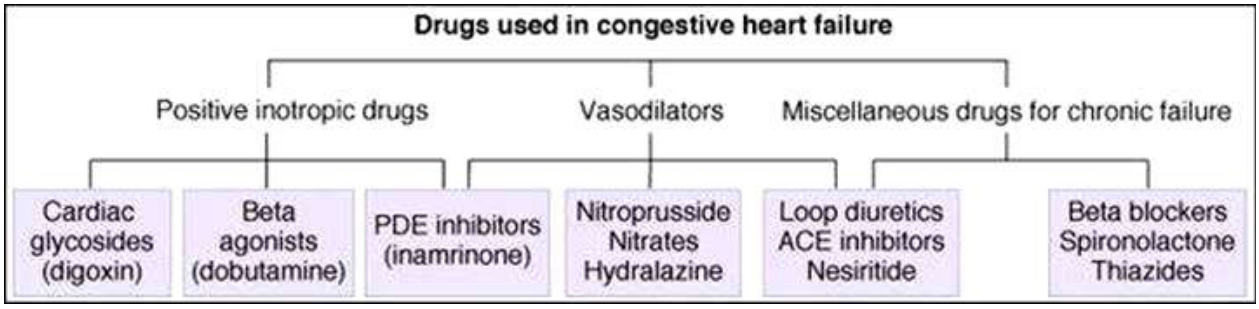
Figure 3. Mechanism of action of clopidogrel.

Uses

- Used to reduce the risk of heart disease and stroke in those at high risk.
- It is also used together with aspirin in heart attacks and following the placement of a coronary artery stent (dual antiplatelet therapy).

DRUGS USED IN CONGESTIVE HEART FAILURE

Congestive heart failure is a condition in which the heart is unable to pump sufficient blood to meet the metabolic demand of the body and also unable to receive it back because every time after a systole. This is the direct result of a reduced contractility of the cardiac muscles, especially those of the ventricles, which causes a decrease in cardiac output, increasing the blood volume of the heart (hence the term " congested"). As a result, the systemic blood pressure and the renal blood flow are both reduced, which often lead to the development of edema in the lower extremities and the lung (pulmonary edema) as well as renal failure. A group of drugs known as the cardiac glycosides were found to reverse most of these symptoms and complications.



Digoxin

- Digoxin is a cardiac glycoside extracted from foxglove leaves (*Digitalis lanata*, Family : *Scrophulariaceae*).
- Digoxin includes a steroid nucleus and a lactone ring; most also have one or more sugar residues. The side chain of digoxin is made up of three molecules of digitoxose in a glycosidic linkage, which upon hydrolysis yields the aglycone, digoxigenin.
- It differs from digitoxin in that it has an additional hydroxyl group at C_{16} of the steroid skeleton.
- The 17- lactone and the steroid (A-B-C-D) ring system are essential for cardiac glycoside activity.

Mechanism of action

- The process of membrane depolarization/repolarization is controlled mainly by the movement of the three ions, Na^+, K^+, Ca^{2+} in and out of the myocardial cells.
- The Na^+/K^+ exchange requires energy and is catalyzed by the enzyme Na^+/K^+-ATPase.

- Digoxin inhibits Na^+/K^+-ATPase enzyme, with a net result of reduced sodium exchange with potassium (i.e. increased intracellular sodium), which in turn results in increased intracellular calcium.
- Elevated intracellular calcium concentration triggers a series of intracellular biochemical events that ultimately result in an increase in the force of the myocardial contraction, or a positive inotropic effect.
- Digitalis also modifies autonomic outflow, and this action has effects on the electrical properties of the heart.

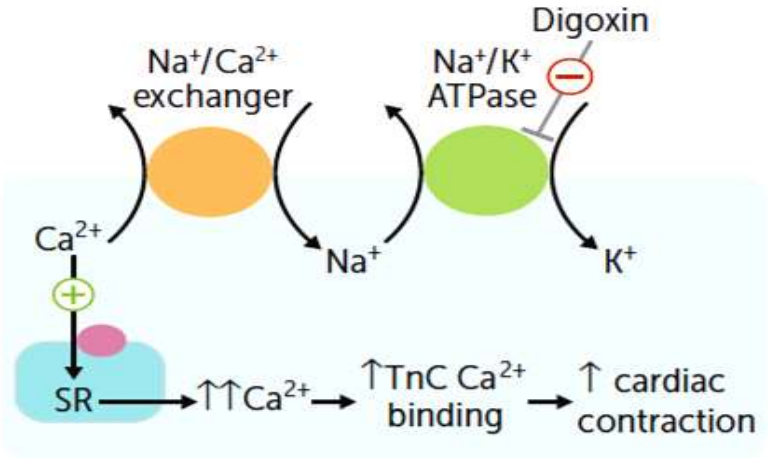


Figure 4. Mechanism of action of digoxin.

Uses

- It is the drug of choice for "low output HF" due to HT, IHD or arrhythmias.
- Treatment of paroxysmal supraventricular tachycardia (arrhythmia due to reentry phenomenon taking place at SA or AV node).
- Treatment of atrial flutter and atrial fibrillation.
- It is helpful in restoring cardiac compensation.
- Digitalis glycosides are no longer considered first-line drugs in the treatment of heart failure.

Digitoxin

- Digitoxin is a lipid soluble cardiac glycoside obtained from *Digitalis purpurea*, *Digitalis lanata* and other suitable species of Digitalis.
- It is a phytosteroid and is similar in structure and effects to digoxin.

- Its side chain is comprised of three molecules of digitoxose in a glycosidic linkage.
- Its hydrolysis affects removal of the side chain to yield the aglycone, digitoxigenin.
- It has a longer half-life than digoxin.

Mechanism of action

Refer the mechanism of action of Digoxin.

Uses

- Digitoxin is used for chronic cardiac insufficiency, tachyarrhythmia form of atrial fibrillation, paroxysmal ciliary arrhythmia, and paroxysmal supraventricular tachycaria.
- It is eliminated hepatically making it useful in patients with poor or erratic kidney function.
- Digitoxin lacks the strength of evidence that digoxin has in the management of heart failure.

Nesiritide

- Nesiritide is a recombinant human B-type natriuretic peptide (BNP).
- It is identical to the endogenous hormone produced in *E. coli.*
- It is a new drug class for the treatment of congestive heart failure.

Mechanism of action

- Human B-type natriuretic peptide (BNP) is normally produced by the ventricular cardiomyocytes.
- Human BNP binds to the particulate guanylate cyclase receptor of vascular smooth muscle and endothelial cells, leading to increased intracellular concentrations of guanosine 3', 5'-cyclic monophosphate (cGMP) and smooth muscle cell relaxation.
- cGMP serves as a second messenger to dilate veins and arteries.
- Nesiritide mimics the actions of endogenous BNP by binding to and stimulating receptors in the heart, kidney and vasculature.
- Nesiritide has venous, arterial, and coronary vasodilatory properties that reduce preload and afterload, and increase cardiac output without direct inotropic effects.

Uses

- For the intravenous treatment of patients with acutely congestive heart failure who have dyspnea at rest or with minimal activity.

Bosentan

- Bosentan is an oral dual endothelin receptor antagonist.
- It is a sulfonamide-derived compound.

Mechanism of action

- Bosentan is a specific and competitive antagonist at endothelin receptor types endothelin A (ET_A) and endothelin B (ET_B).
- It has slightly higher affinity for the ET_A receptor than endothelin ET_B.
- Endothelin 1 is an extremely potent endogenous vasoconstrictor and bronchoconstrictor. Bosentan blocks the action of endothelin 1 by binding to endothelin A and endothelin B receptors in the endothelium and vascular smooth muscle.
- Thus Bosentan decreases both pulmonary and systemic vascular resistance.

Uses

- It is used in the treatment of pulmonary arterial hypertension (PAH).
- It is used to reduce the number of active digital ulcers.

Tezosentan

- Tezosentan is an intravenous endothelin receptor A/B antagonist.
- It has pyridinylpyrimidine skeleton.

Mechanism of action

- Tezosentan competitively antagonizes the specific binding of endothelin-1 (ET-1) and endothelin-1 (ET-3) on cells and tissues carrying ET_A and ET_B receptors.
- This results in vasodilatory responses leading to an improvement in cardiac index.

Uses

- It acts as a vasodilator and was designed as a therapy for patients with acute heart failure.
- It is used to treat pulmonary arterial hypertension.

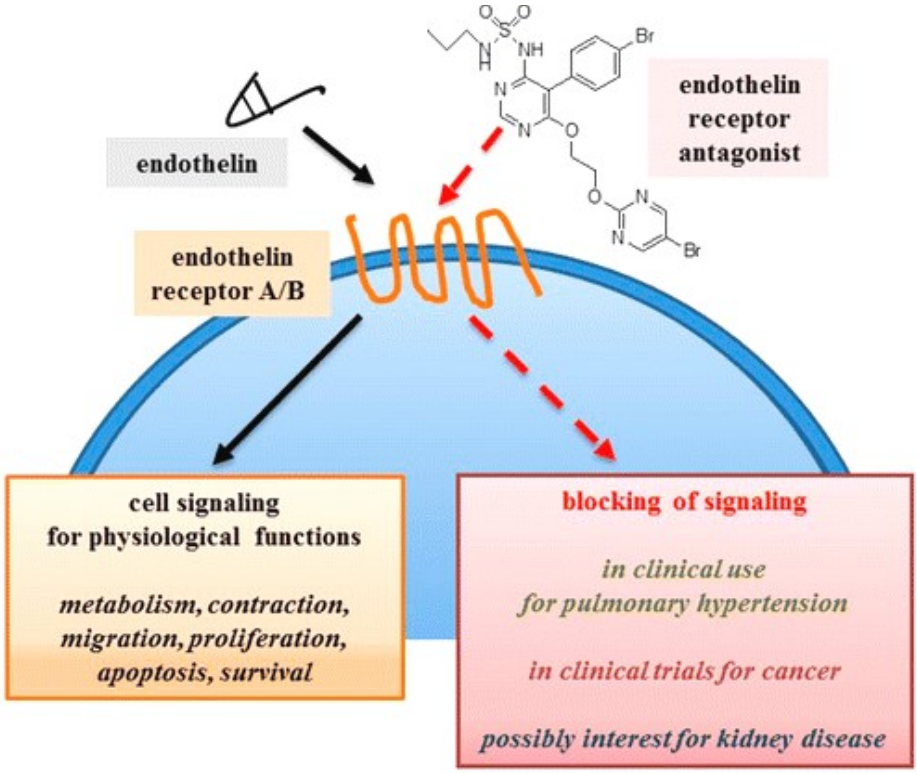


Figure 5. Mechanism of action of tezosentan.

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