CHAPTER
CARDIOVASCULAR DRUGS

The American Heart Association estimates that greater than 50% of deaths are related to some form of cardiovascular disease, and many of these may be effectively prevented by appropriate external intervention. Cardiovascular drugs can be broadly categorized as 1) anti-anginals, 2) anti-arrhythmics, 3) anti-hypertensives, 4) anti-coagulants, 5) anti-hyperlipidemic agents, 6) hypo-glycemic agents, and 7) anti-thyroid drugs and thyroid hormones. This chapter includes a discussion of the first four categories.

ANTI-ANGINAL DRUGS

Introduction

Anti-anginals are pharmaceutical agents used to treat angina pectoris, a disease of the coronary arteries. The coronary arteries supply oxygen-laden blood from the left ventricle to all heart muscles including those of the ventricles themselves. Coronary arteries maintain cardiac function and are expected to adapt to sudden demands on the heart due to enhanced activity. Typically the arteries respond to this sudden demand by dilatation. However, it is possible that they may have developed atheromatous deposits that restrict the flow of blood even under normal conditions and more so under strenuous activity. The heart has to exert more to increase the blood flow through such atheroslerotic arteries. In this situation the heart is deprived of oxygen and feels suffocated, a condition called *ischemic*. Angina is the principal symptom of an ischemic heart creating a sudden, severe pain that originates in the chest and radiates through the left shoulder down the arm.

Types of Anti-anginal Drugs

There are three classes of agents that relieve anginal pain: *organic nitrates* and *calcium channel antagonists* are indicated in spasmatic and chronic stable angina, while *β-adrenergic antagonists* are primarily for exertion-induced angina. Anti-anginal agents mainly alleviate the pain by reducing the oxygen requirements of the heart, thereby

reducing anginal pain. Each class of anti-anginal agent utilizes a distinct mechanism for reducing the heart workload and consequently may be simultaneously used to increase the therapeutic effect.

Organic Nitrates

Organic nitrates are also called nitrovasodilators. Amyl nitrite, **1.,** was the first anti-anginal agent discovered in 1867. Several organic nitrates with varying potency are now available for clinical use. Although newer agents such as the calcium channel antagonists and β-adrenergic antagonists have been introduced, organic nitrates remain the drugs of choice for treating spasmatic episodes of angina.

Chemistry:

Nitrovasodilators are small nitrate or nitrite esters of simple organic alcohols, whereas normal organic esters, e.g. RCOOR', are a combination of an organic acid (RCOOH) with an organic alcohol (R'OH), The nitrovasodilators are esters of nitrous (HNO_2) or nitric (HNO_3) acid with an organic alcohol, Figure 1. It is important to note that all nitrate (nitrite) esters consist of an O-N bond, and not a C-N bond. The common name nitroglycerine, **2.**, suggesting the presence of a nitro group (NO_2) attached to an alkyl carbon, is a misnomer and should be more appropriately called glyceryl trinitrateisoamyl nitrite. Also amyl nitrite consists of an isoamyl group and should be more correctly called isoamyl nitritie.

As can be seen from structures **1-5**, the nitrovasodilators are small uncharged organic molecules. A specific advantage results from this characteristic. Because of their non-polar nature these agents exhibit very high lipid permeability. Thus rapid treatment of acute anginal episodes is possible through fast absorption relieving the patient of severe pain. Most agents are fairly volatile causing some concern in handling. Being esters, nitrovasodilators are susceptible to hydrolysis and hence long-term storage is a concern due to loss of activity. Preparations of these agents should be protected from moisture. In addition, these nitrate esters also exhibit potential for explosion. Thus many are available in diluted forms in the presence of excipients that minimize the potential for hazardous explosion.

Pharmacokinetics

The onset and duration of action of these agents is dependent on the structure of the molecules. The smallest agent amyl nitrite, a gas, can be inhaled and hence is the one that shows almost instantaneous effect upon administration (30 seconds). Although sublingual and oral modes of administration are available, in general, the larger the molecule and more sterically hindered the nitrate group, the longer the onset and the duration of action. Thus glyceryl trinitrate and isosorbide dinitrate, **3.**, have a shorter onset time (< 5 minutes) in comparison to erythrityl tetranitrate and pentaerythritol tetranitrate (15→30 minutes). Similarly, the duration of action changes from 30-60 minutes for smaller molecules to 3-5 hours for the larger molecules.

Metabolism

Organic nitrates are rapidly metabolized by first pass metabolism in the liver and also extra-hepatic tissues such as blood stream, kidneys, lungs, and intestinal mucosa. The metabolism of the organic nitrates is the principal reason for their action as anti-anginal agents. In this process, the organic nitrates react with cysteine-containing proteins resulting in the release of nitric oxide, NO, that is responsible for the vasodilating effect on the arteries. Thus, the parent organic nitrates do not possess inherent anti-anginal activity and can be viewed as pro-drugs, agents that release the therapeutically active entity in the human body. Both chemical and enzymatic processes release NO *in situ* from the nitrovasodilators. Chemical agents such as cysteine react with organic nitrates to form S-nitrosothiols (R-S-NO) that decompose rapidly to release NO, while glutathione-nitrate reductase is a specific enzyme that reduces the organic nitrates to nitrites that subsequently release NO non-enzymatically.

Biochemical Mechanism of Action

Figure 2 depicts the biochemical events that regulate the contraction and relaxation function of all muscle (smooth, cardiac, skeletal). The state of muscle (contraction or relaxation) is controlled by the action of myosin-actin pair of proteins. Depending on whether myosin is phosphorylated or not, the action of actin results in either contraction or relaxation of the muscle. The nitric oxide released by nitrovasodilators activates

guanylate cyclase an enzyme that produces cGMP. Increase in the concentration of cGMP, in turn, activates protein kinases that phosphorylate MLCK, thus preventing the phosphorylation of myosin and resulting in muscle relaxation, Figure 2. Muscle relaxation, or vasodilation, results in reduced workload for the heart, thus easing anginal pain.

Calcium channel antagonists

As evident from the above discussion on the simplified mechanism of muscle contraction cellular levels of free Ca^{+2} ions play an important role. Thus, one may can envisage that molecules that block the passage of Ca^{+2} ions from the outside to the inside of the muscle cell, Figure 2, will also prevent the contraction of muscles leading to reduced work load and hence lowered oxygen requirement. Out of four different types of calcium channels, an L-type channel, named for its long-lasting nature, is principally responsible for the inward current of divalent calcium ions into skeletal, cardiac and muscle cells. Calcium channel antagonists that bind these L-type channels cause antagonism and are effective as anti-anginal agents. These agents do not physically block the channel, but bind at specific sites in the open form of the channel.

Chemistry

Three classes of calcium channel blockers are currently approved for use in the prophylactic treatment of angina: the dihydropyridines, **6a-c.,** the benzothiazepines represented by diltriazem, **7.**, and the aralkylamines, **8a,b.** No structural similarities exist between the three classes of compounds suggesting that the activity profile of each class is distinct from the other. Nifedipine,**8a**, amlodipine, **8b.**, and nicardipine, **8c.**, belong to the dihydropyridine class of Ca^{+2} channel blockers. These have a substituted pyridine ring that is partially saturated as a central common feature. Diltiazem belongs to the benzo[*b*-1,5]-thiazepine family, seven membered ring containing nitrogen and sulfur atoms fused with an aromatic ring. Verapamil, **8a.** and bepridil,**8b.**, have only one thing in common, an amine group substituted with an alkyl and an aryl group. Arylalkylamines have a chiral center, where the dextrorotatory isomer is more active than its counterpart.

Metabolism

Each calcium channel blocker contains an amine group facilitating the preparation of its hydrochloride salt administered as oral tablets and capsules. Also these agents have a predominantly hydrophobic structure explaining their rapid and complete absorption after oral administration. In fact nearly 75-95% of the drug is found in the blood stream. Most of these agents exist primarily in the protein bound (80-95%) state in the plasma, although they are active in the free form. The duration of action ranges from 4 to 8 hours for most agents except for amlodipine that has a 24 hour duration of action due to the presence of the chlorine atom.

First-pass metabolism of verapamil, diltiazem, incardipine and nifedipine is extensive resulting in low bioavailability. Verapamil is converted into the norverapamil in which the nitrogen has been N-demethylated. Norverapamil is only about 20% as active as the parent active molecule. Extensive O-demethylation also occurs rapidly giving inactive metabolites. Diltiazem is metabolized by the action of esterases to its desacetyl derivative that has only about 50% its activity. Other *N*- and *O*-demethylations result in inactive metabolites. The dihydropyridines are mostly metabolized to inactive species in which the phenyl group has been extensively hydroxylated.

β-Adrenergic Antagonists

Propranolol, **9.**, is a common nonselective β-blocker of both cardiac and bronchial adrenergic receptors. It is typically used for exertion-induced angina which originates from coronary atherosclerosis. Drugs with β-blocking activity slow the heart rate and decrease the force of contraction of muscles, thus these drugs are useful in treating hypertension and cardiac arrythmias, in addition to angina. Propanolol is also typically used in combination with organic nitrates or calcium channel blockers to enhance its anti-anginal efficacy.

ANTI-ARRHYMTHIC AGENTS

Introduction

Arrhythmia is a disease in which the rhythmic contraction of the heart is disturbed or altered. Rhythmic contractions are caused by a sequence of electrical activity

propagating through the myocardial tissue that engulfs the heart. These contractions are controlled by the pacemaker cells of the heart, or by the S-A node. On the release of the impulse from the S-A node, the impulse spreads to the entire myocardium through specialized automatic fibers. This spreading of the impulse produces the characteristic electrocardiogram pattern, Figure 3, that represents the changes in membrane action potentials brought about by alterations in the sodium, potassium, calcium and chloride ion concentrations within the cells.

Mechanism of Arrhythmias

Cardiac arrhythmias can originate from a disturbed origin of the impulse, i.e., pacemaker cells. These cells may have altered automaticity, the rhythmic property to effect membrane depolarization at an optimal rate. Disturbed automaticity of pacemaker cells may arise from underlying diseases such as hypertension, atherosclerosis, hyperthyroidism, or lung disease. Other forms of arrhythmias may be caused by origination of impulses in cells other than pacemaker cells. These are called ectopic arrhythmias. The underlying causes of ectopic arrhythmias are myocardial ischemia, excessive myocardial catecholamine release, or toxicity of cardiac glycosides. Arrhythmias are also produced when the electrical impulse does not die down completely before the beginning of phase 0. In such circumstances, a fraction of previous impulse that remains at the end, re-enters and re-excites the heart muscles pre-maturely resulting in asynchronous depolarization. This is the characteristic form of pre-mature heartbeat. Re-entrant arrhythmias are common in coronary atherosclerosis.

Classes of Anti-arrhythmic Drugs

Anti-arrhythmic agents can be placed in four classes depending on their mode of action or the effect that they produce on the electrocardiogram, Table 1. Class I drugs are generally local anesthetics that act on membranes to depress the maximal rate of depolarization, i.e., that slow down the conduction of the impulse. These drugs are further sub-classified into three groups based on their effect on the length of the action potential (QT interval, Figure 3). Class IA drugs increase, class IB decrease while class IC drugs do not change the duration of action potential. All agents in class I bind to the

fast Na^+ channel and interfere in the process of depolarization. The Na^+ channel can exist in three distinct states, resting, opened or closed. The affinity of class I agents for these three states are different resulting in differential effects on the duration of action potential.

Class II drugs are β-adrenergic blocking agents that stabilize the membrane or block the adrenergic enhanced phase 4 depolarization. These agents decrease the neurologically initiated automaticity. Thus the effects of ectopic pacemaker cells are depressed resulting in slowing down of heart rate. Class III drugs prolong the duration of action potential without altering the maximal rate of depolarization (MRD) or the resting potential. Drugs in this class act through many mechanisms that involve Ca^{+2}, K^+, and Cl^- transport. Class IV drugs are Ca^{+2} channel blockers possessing anti-arrhythmic activity. These agents block the slow movement of Ca^{+2} ions during phase 2, lengthening the duration of the action potential.

Drugs belonging Class IA

Quinidine, 10.

Quinidine is a dextrorotatory diastereoisomer of quinine. Both quinidine and quinine are obtained from many species of *Cinchona* plant. Quinidine contains two basic nitrogens, of which the quinuclidine nitrogen has a pKa of ~10 and is thus more basic. Quinidine is a prototypic anti-arrhythmic drug that reduces Na^+ ion current by binding to the open ion channel resulting in depression of automaticity of ectopic foci. It is used to treat supraventricular and ventricular ectopic arrhythmias, atrial and ventricular tachycardia, atrial flutter and atrial fibrillation.

Quinidine is available as a sulfate, or gluconate, or polygalacturonate. Each possesses slightly different physical and bio-absorption properties. Quinidine sulfate is an oral preparation that can be used intramuscularly. It is rapidly absorbed from the GI tract and onset of action begins in about 30 minutes. Quinidine gluconate is soluble in water and is mostly used in emergencies when rapid response may be needed that make oral administration of quinidine sulfate ineffective. Quinidine polygalacturonate gives more stable and uniform blood levels of quinidine.

Procainamide, **11.**

Procainamide hydrochloride has emerged as a major anti-arrhythmic drug in the treatment of cardiac arrhythmias. Procainamide is more stable in water in a wide pH range (2–7) than typical amide bond containing molecules. Metabolism of procainamide results in N-acetylprocainamide that possess only 1/4th the activity of the parent drug. Unlike quinidine, procainamide is bound to serum albumin to significantly less extent, although it is rapidly absorbed (75-95%) from the GI tract.

Disopyramide, 12.

Disopyramide is an oral and intravenous agent that is similar to quinidine and procainamide in its effect and mechanism of action. Oral administration produces peak concentrations within 2 hr while only 50% is bound to serum proteins.

Lidocaine, 13.

Lidocaine is a class IB anti-arrhythmic drug that was initially introduced as a local anesthetic, but is now routinely used intravenously for treatment of arrhythmias arising from acute myocardial infarction and cardiac surgery. Lidocaine binds to both active and inactive Na^+ channels with nearly equivalent affinity causing depression in diastolic depolarization and automaticity. Lidocaine does not bind to serum proteins to a significant extent because it is significantly positively charged at the physiological pH. It is rapidly metabolized in first pass metabolism. The monoethylglycinexylidide metabolite, resulting from partial de-ethylation of the *N*-di-ethyl group, is an effective anti-arrhythmic agent. Lidocaine has a half-life of 15 to 30 minutes. Lidocaine solutions containing epinephrine are strictly used for local anesthetic purposes.

Phenytoin, 14.

5,5-diphyenylhydantoin has been traditionally used in the control of grand mal type epileptic seizures. Phenytoin is structurally analogous to the barbiturates but does not possess their sedative effects. Phenytoin is clinically used in the treatment of digitalis-induced arrhythmias and its action is similar to that of lidocaine.

Mexiletine, 15.

This is a class IB anti-arrhythmic drug with properties similar to lidocaine, however with one significant difference. Whereas lidocaine is an amide that is susceptible to hydrolysis, mexiletine is an ether that retains stability under most conditions. Thus mexiletine has a prolonged half-life on oral administration of nearly 10 h. Metabolism of mexiletine produces p-hydroxy and hydroxymethyl derivatives that are not active.

Tocainide, 16.

This drug is an analogue of lidocaine with similar properties. It is a primary amine rather than the tertiary amine that lidocaine is, and thus has a lower pKa of 7.7 in comparison to lidocaine's ~9.5. Tocainide is not subject to first pass metabolism because of its low hepatic clearance. However, like lidocaine its metabolite, p-hydroxy xylyl derivative, is inactive. It is used orally for treatment of ventricular ectopy and tachycardia.

Encainide, 17. and Flecainide, 18.

Both these drugs are class IC anti-arrhythmic agents (Fig. 9) that depress the rate of depolarization and increase the length of refractoriness. Both are benzanilide derivatives. As with procainamide, both possess local anesthetic properties. Encainide is extensively metabolized into active products. The metabolite, 3-methoxy-O-demethyl-encainide (MODE, 3-methoxy-N-[2-[2-(1-methyl-2-piperidinyl)ethyl]phenyl]benzamide), is nearly as potent as the parent drug, while O-demethyl-encainide (ODE, 4-hydroxy-N-[2-[2-(1-methyl-2-piperidinyl)ethyl]phenyl]- benzamide) is more potent. Both MODE and ODE can persist in the plasma for as long as 12 hours, while encainide has a half-life of only 2-4 hours. Metabolism of flecainide results in meta-O-dealkylated product with 50% less activity than the parent drug. Flecainide in the acetate form can be given orally.

Lorcainide, 19.

This drug is an acetamide derivative, rather than benzamide derivative, and possessess local anesthetic activity in addition to class IC anti-arrhythmic activity. Metabolism of the drug produces N-dealkylated product, norlorcainide, on first pass

metabolism. Norlorcainide is an important metabolite because it persists in the plasma much longer than lorcainide and is equally active as the parent drug.

Moricizine, 20.

This drug is a phenothazine derivative class IC antiarrhythmic agent that blocks the Na^+ channel. Moricizine possesses higher affinity for the inactivated state than the activated or resting state of the Na^+ channel. It is used almost exclusively for life-threatening ventricular arrhythmias.

Propafenone, 21.

Although this drug contains a chiral center, it is sold as a racemic mixture. Both the (R)- and (S)- enantiomers exert Na+ channel blocking effect, but the (S)- also exerts β-adrenergic effect. Combined, the (S)-isomer produces nearly 40-fold greater anti-arrhythmic effect than the (R)-enantiomer. Metabolism of both enantiomers produces 5-hydroxy metabolites that as active as the parent compounds. Bioavailability is estimated at less than 20% due to first pass metabolism.

Sotalol, 22.

This drug is sold as a racemic mixture although the *d(+)*-enantiomer only, possesses class III activity. The *l(-)*- isomer has both class II (β-adrenergic blockade) and III (K^+ channel blockade) activity. Thus the isomers produce slightly different effects on the slowing of heart rate. Sotalol is not bound to plasma proteins and is excreted unchanged through renal excretion mechanism.

Amiodarone, 23.

Amiodarone was introduced as an anti-anginal agent, but has a pronounced anti-arrhythmic action. Amiodarone lengthens effective refractory period. The drug has a very slow onset of action (days) and is eliminated very slowly from the body, with a half-life of approximately a month following oral doses. This drug has iodine atoms in its structure and hence affects thyroid hormones. Hypothyroidism occurs in up to 11% of

patients. In addition, it inhibits enzymes of oxidative system and hence interferes with the normal metabolism of other drugs.

Bretylium tosylate, 24.

This drug is a quaternary ammonium salt that is extremely soluble in both water and alcohol. Bretylium tosylate is an adrenergic neuronal blocking agent that accumulates in the neurons and displaces norepinephrine. Because of this it was earlier used as an antihypertensive agent, but its use was discontinued due to development of tolerance and pain related side effects. It prolongs effective refractory period but does not affect the rate of depolarization and hence is classified as a class III agent. The precise mechanism of action of bretylium tosylate remains to be elucidated.

Verapamil, 7. and Diltiazem, 8a.

Both these drugs block the slow inward movement of Ca^{+2} ions causing a slowdown of the conduction. These drugs are used in controlling atrial and paroxysmal tachycardias. Both are extensively bound to plasma proteins.

ANTI-HYPERTENSIVE AGENTS

Introduction

Hypertension, or high blood pressure, is the most common of all cardiovascular diseases with nearly 40 million people affected in the US alone. It is the number one cause of stroke and heart attack. Normal blood pressure is about 120/80 in a healthy adult. People with sustained readings of 140/90 are said to have high blood pressure. Patients with readings as high as 200/120 need treatment immediately. Consistent high blood pressure can damage the brain, eyes, and kidneys. Hypertension is often called "the silent killer" because it rarely exhibits symptoms even as it inflicts serious damage on the body.

Hypertension is referred to as essential, or primary, when a specific cause cannot be identified. This is the most common type of high blood pressure, occurring in up to 95% of patients. Genetic factors appear to play a major role in essential hypertension. These

include genes that regulate a group of hormones known collectively as the angiotensin-renin system, and that regulate the sympathetic nervous system.

Secondary hypertension has recognizable causes that can be independently treated or reversed. Medical conditions that contribute to temporary hypertension are pregnancy, cirrhosis, kidney disease, or Cushing's disease. Certain prescription and over-the-counter medications can cause the blood pressure to rise. Abuse of alcohol leads to hypertension in some 10% of cases, although moderate drinking is perhaps beneficial. Drinking excessive coffee increases excretion of calcium that plays an important role in blood pressure etiology. Temporary high blood pressure can also be caused from stress and exercise.

Drug Therapy

Numerous anti-hypertensive drugs are currently available. They can be categorized into: 1) Angiotensin – converting enzyme inhibitors, that reduce the production of angiotensin-II and -III, chemicals that cause arterioles to constrict; 2) sympathetic nervous system depressants including vasodilators and calcium channel blockers, each of which cause dilatation of blood vessels resulting in reduction of peripheral vascular resistance, and 3) diuretics that cause the body to excrete water and salt, producing anti-hypertensive effects. Calcium channel blockers (β-blockers) and diuretics have been discussed earlier and hence will not be repeated here.

The Renin-Angiotensin System

The renin-angiotensin system is a hormonal regulatory mechanism controlling the excretion of sodium and maintains body fluids. It is closely connected with the sympathetic nervous system and biosynthesis of aldosterone. Figure 4 shows the relationship of the renin-angiotensin system with the physiological effect of blood pressure control. Lowering of blood pressure results in the release of renin, an aspartyl protease that cleaves angiotensinogen, a plasma glycoprotein. This releases angiotensin-I, a decapeptide, from the carboxy terminal end of angiotensinogen. Angiotensin-I is further cleaved at its carboxy terminal end to form an octapeptide, angiotensin-II, by angiotensin-converting enzyme (ACE). Angiotensin-II is the first

peptide that is a potent vasoconstrictor. The release of angiotensin-II thus results in an increase in blood pressure. Further reaction of angiotensin-II with glutamyl aminopeptidase results in angiotensin-III that is slightly less potent as a vasoconstrictor but possesses significant regulatory effect on sodium excretion. Thus, action of ACE increases the secretion of angiotensin-II and -III, constricting peripheral blood vessels, thereby raising blood pressure. Further, angiotensins-II and -III increase the secretion of aldosterone causing enhanced sodium retention resulting in increased blood pressure.

Angiotensin–converting enzyme (ACE) is a membrane bound enzyme that utilizes zinc for optimal enzymatic hydrolysis of the second peptide bond from the carboxyl terminus of a polypeptide. The minimum structural requirement for binding and cleavage of a substrate by ACE is that it should be a tripeptide with a free carboxylate group. A general exception is that peptides with a penultimate prolyl residue are not cleaved. This accounts for the stability of angiotensin II. As expected, inhibitors to ACE decrease the synthesis of vasoconstrictors resulting in the lowering of the blood pressure.

Angiotensin–converting enzyme (ACE) Inhibitors

Captopril, 25. and Lisinopril, 26.

These drugs are ACE inhibitors containing a carboxylate group that recognizes the cationic site, arginine, in active site of the enzyme. The thiol group was incorporated in captopril in the hope of enhancing its binding to zinc, however it introduces some side effects such as rashes and loss of taste. Both agents are stoichiometric inhibitors. Lisinopril is a lysine derivative and its metabolite, enalaprilat, is active.

Enalapril, 27., Benazepril,28., Quinapril, 29. and Ramipril, 29.

Each of these drugs functions as an ACE inhibitor prodrug. They contain a 2-(S)-aminophenylbutryic acid ethyl ester moiety. These drugs are converted to the active enzyme inhibitor following absorption and metabolism by liver and intestinal enzymes. The ester moiety has to be hydrolyzed by a nonspecific esterase and hence typically these are long lasting drugs. Each of these drugs is used in mild to moderate hypertension state, either alone or in combination with diuretics or calcium channel

blockers. While enalapril is available as a maleate salt, benazepril and quinapril are available as hydrochorides. Fosinopril, **31.**, is the only ACE inhibitor that contains a phosphorus atom.

Direct-Acting Vasodilatory Drugs

Drugs that act directly to induce dilation of the smooth muscle cells are useful in treatinf hypertension. These include hydralazine, **32.**, sodium nitroprusside, **33.**, calcium channel blockers and potassium channel openers.

Hydralazine

This drug is useful in the treatment of moderate to severe hypertension and is used in combination with other anti-hypertensive drugs. It dilates the vascular smooth muscle fibers as a result of its action on the cells, reducing the resistance to blood flow and thus decreasing the pressure. Additionally, it improves renal blood flow and thus is especially useful for patients with renal dysfunction. Its exact mechanism is unknown. Hyralazine is a stable yellow solid with low water solubility (~3%). It reaches peak plasma concentration within 1 hour and is rapidly metabolized by benzylic oxidation, glucuronidation and N-acetylation. It is available as a drug in its hydrochloride form.

Sodium nitroprusside, 33.

Sodium nitroferricyanide is one of the most potent blood pressure lowering drug, however it is useful only in emergencies because of its short action span. Dilatation of both the arterial and venous smooth muscle cells occurs. The exact mechanism remains unknown, however the physiological effect arises due to its decomposition and formation of nitric oxide in the plasma.

Diazoxide, 34. and Minoxidil, 35.

Both these drugs are potassium channel agonists that decrease the concentration of Ca^{+2} ions within the cells and thus reduce the excitability of the smooth muscle cells. Diazoxide lowers the peripheral vascular resistance, and so does minoxidil. However, minoxidil requires activation by sulfotransferase to minoxidil sulfate before it becomes

functionally active. Diazoxide is intravenous injection at pH 11.5 that converts the drug to its soluble sodium form. The drug is highly protein bound and can displace other drugs. Minoxidil is useful in severe hypertension that is difficult to control with other drugs.

ANTICOAGULANTS

Introduction

The blood circulatory system has to be self-sealing, otherwise continued blood loss from even the smallest injury would be life threatening. Normally, all but the most catastrophic bleeding is rapidly stopped, in a process known as hemostasis. Hemostasis is a combination of many events arising from physical and chemical interactions between soluble components of the plasma, the vascular bed and cellular material. The final result of these interactions is the formation of a highly cross-linked insoluble hard mass containing cells, enzymes, and other proteins at the site of injury that prevents blood loss as well as ingress of microbes into the vasculature. This hard mass is blood clot, medically known as thrombus. Clot formation may also occur within the vasculature and without any external injury. Intravascular clotting or thrombosis can be caused by vascular injury or blood hypercoagulability.

Physical Forces in Clotting

Upon injury to the vascular wall, the sub-endothelial cells are exposed. This sets off a series of responses. First a reduction in the blood flow occurs (vasoconstrictive reflex) that allows platelets to adhere to the injured cells at the site of injury (platelet adhesion) Figure 5. Simultaneously, certain chemicals that facilitate platelet aggregation are released by platelets. These processes called platelet release and platelet aggregation lead to the formation of a platelet plug, a mass of platelets held together by physical non-covalent forces and susceptible to rupture for shear forces, for example from rapidly flowing blood. The platelet plug is reinforced by the formation of fibrin, a three-dimensional covalent network of polypeptide chain, in a process called coagulation cascade.

Chemical Forces in Clotting

The clotting cascade is a sequence of chemical reactions mediated by enzymes present in the plasma. The cascade is traditionally described as the intrinsic and the extrinsic pathways Figure 6. The intrinsic pathway is defined as a cascade that utilizes only factors that are soluble in the plasma, whereas the extrinsic pathway consists of some factors that are insoluble in the plasma, e.g., membrane-bound factors (factor VII). However, the boundary differentiating these two is becoming more and more blurred.

The distinguishing feature of the coagulation cascade is that activation results in an enzyme that converts the pro-enzyme (zymogen form) in the next step to an active enzyme. The newly formed enzyme then acts further down the cascade to greatly amplify the initial activation signal. The activated forms of the proteins are identified by symbol '**a**'. These reactions occur in the presence of Ca^{+2} cations and on an appropriate phospholipid membrane.

Both the intrinsic and the extrinsic coagulation pathway merge at the formation of factor Xa which in turn cleaves prothrombin at two sites to yield a very important enzyme of the clotting cascade, thrombin. Thrombin possesses numerous properties, chief among them are the coagulation and anti-coagulation activities. Under appropriate conditions, thrombin cleaves fibrinogen that constitutes nearly 2-3% of plasma protein. Fibrinogen cleavage results in soluble fibrin monomers that spontaneously aggregate to form a soft clot. This aggregate is rapidly converted to a more stable "hard clot" by the covalent cross-linking of neighboring fibrin molecules in a reaction catalyzed by fibrin-stabilizing factor (FSF or factor XIIIa). The process of three-dimensional crosslinking that occurs in the polymeric fibrin formation traps numerous cells including red blood cells and platelets.

Anti-coagulants

Anti-coagulants are molecules that prevent blood from clotting. They inhibit the chemical process of proteolytic formation of the three-dimensional fibrin polymer. These include heparin, low molecular weight heparin, coumarins, and 1,3-indanediones.

Molecules that do not allow platelets to aggregrate and thus prevent clotting, especially in the arteries, are called anti-platelet agents. These include aspirin, sulfinpyrazone, dipyridamole, and ticlopidine. Molecules that disintegrate a pre-formed clot are called fibrinolytic agents. A typical example in this category is the enzyme, streptokinase.

Anticoagulants are indicated in myocardial infarction, venous thrombosis, peripheral arterial emboli, pulmonary embolism and many other conditions. Anticoagulants are also used in blood transfusions, extracorporeal blood circulations and dialysis procedures. Let us discuss the structural, functional, and physicochemical aspects of clinically used anti-coagulant drugs.

Heparin

Heparin is a strongly acidic, high molecular weight mucopolysaccharide that possesses rapid anticoagulant effect. Heparin, prepared from bovine lung mucosa or porcine intestinal mucosa, is a mixture of compounds of varying molecular weight and chemical structure. It is a linear polysaccharide composed of alternating residues of glucosamine and uronic acid that are linked to each other in a $1\rightarrow4$ manner, Figure 7. A typical preparation of heparin may have polysaccharide chains in the range of nearly 10 – 100 monosaccharide residues corresponding to a M_W range of 3,000 – 30,000.

The uronic acid residues may be of β-D-glucuronic or α-L-iduronic type. The β-D-glucosamine residues are typically either sulfated ($-OSO_3^-$) or acetylated ($-COCH_3$) at the 2-position. The available hydroxy groups, the 2-OH in iduronic acid and 6-OH in β-D-glucosamine, may be sulfated. The numerous negatively charged groups ($-COO^-$ and $-OSO_3^-$) that span the entire length of the linear polysaccharide give a strongly acidic character to this molecule. In fact heparin is the strongest acid in our body. The polyanionic character of heparin, coupled with its structural microheterogeneity and the polydispersity mentioned above, is probably the single source of its numerous adverse effects.

Low molecular weight (LMW) heparins obviate some of these adverse effects. LMW heparins, prepared by either chemical or enzymatic depolymerization of full-length heparin, have a M_W range of 4,000–8,000 with an average of 5,000 corresponding to about 15 monosaccharide residues. Reduction in the M_W significantly reduces their

negative charge density thereby lowering their non-specific interactions with plasma proteins and cells. However, the chemical and enzymatic methods used to prepare LMW heparins may introduce additional structural variations to increase the heterogeneity of the commercial preparations.

The key structural unit of heparin is a unique pentasaccharide sequence, Figure 8. This sequence consists of three D-glucosamine and two uronic acid residues. The central D-glucosamine residue contains a unique 3-*O*-sulfate moiety that is rare outside of this sequence. Four sulfate groups on the D-glucosamines (Figure 8) are found to be critical for retaining high anticoagulant activity. Elimination of any one of them results in a dramatic reduction in the anticoagulant activity. Removal of the unique 3-*O*-sulate group results in complete loss of the anticoagulant activity. Removal of sulfate groups other than the critical ones seems to insignificantly affect the anticoagulant activity. Only a third of the chains in commercial heparin preparations have this unique pentasaccharide sequence. Thus, more than 2/3rd of heparin chains are probably not active as anticoagulants. LMW heparin preparations may have considerably varying proportion of chains with the active site.

Properties of Heparin

Because of its highly acidic sulfate groups, heparin (or LMW heparins) exists as a polyanion at physiologic pH. The heparin polysaccharide chain is degraded in the gastric acid and must therefore be administered intravenously or subcutaneously. LMW heparin, because of its smaller size, is more bioavailable when given subcutaneously. Heparin is typically not given intramuscularly because of the danger of hematoma formation. Peak activity of heparin is reached within minutes of administration and is found to last 2-6 h (iv) or 8-12 h (sc). Heparin is relatively non-toxic and can be safely used in pregnancy because it does not cross the placental barrier.

Heparin overdose or hypersensitivity may result in excessive bleeding. If hemorrhage occurs the anticoagulant effect of heparin can be reversed in minutes by administration of protamine sulfate, a low molecular weight protein that has multiple positively charged groups.

Biochemical Mechanism of Heparin Action

The anticoagulant action of heparin occurs through antithrombin, a glycoprotein that exists in our plasma at a fairly high concentration (~2 μM). Antithrombin is an inhibitor of many proteases of the coagulation cascade, especially thrombin and factor Xa, under physiological conditions. Thus antithrombin prevents the conversion of fibrinogen to fibrin thereby inhibiting clotting. However the rate of inhibition of both these enzymes by antithrombin is rather slow (Figure 9). Heparin, containing the unique five-residue sequence (Figure 8) forms a high-affinity complex with antithrombin. The formation of antithrombin-heparin complex increases the rate of inhibition of both factor Xa and thrombin some 500 – 4,000-fold (Figure 9). Heparin chains devoid of the pentasaccharide sequence cannot bind antithrombin tightly and hence do not increase the inhibition of the critical coagulation enzymes. The fact that heparin-antithrombin complex inactivates proteolytically active molecules, thrombin and factor Xa, suggests that heparin action is instantaneous. Accelerated inhibition of factor Xa and thrombin shuts down the coagulation process and is the primary reason for heparin's clinical use as an anticoagulant.

Oral Anticoagulants (Coumarins and 1,3-Indanediones)

Coumarins and 1,3-indandiones are orally active anticoagulants. The first of these active agents, bishydroxycoumarin, has been in use for more than 50 years. Coumarin, a natural product with strong aromatic odor, is a water-insoluble compound containing a lactone moiety while 1,3-indanedione, also aromatic and not soluble in water, has two ketone moieties. Introduction of a 4-hydroxy substitution in the coumarin structure and a 2-aryl substitution in the 1,3-indandione structure improves their water-solubility because of resonance stabilization of the anion formed under alkaline conditions (Figure 10).

Both parent coumarin and 1,3-indandione do not possess any anti-coagulant activities. However, 4-OH and 3-alkyl substitution in the coumarin ring while 3-aryl substitution in the 1,3-indandione ring confers anticoagulant activity. The clinically useful anticoagulants are listed in figure 11. The coumarin derivatives are used for

thrombophlebosis, pulmomary embolism, and coronary thrombosis. Some coumarins have also been used primarily as rodenticide.

Coumarins and 1,3-indandiones have a very slow onset of action. They typically exert their effects in vivo only after about 24 to 48 h and their duration of action is also much longer, ~1.5 to 5 days. The reason for this difference is activity lies in their biochemical mechanism of action.

Biochemical Mechanism of Action of Coumarins and 1,3-indandiones

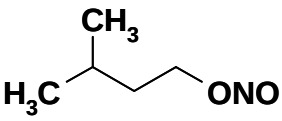
Coumarins and 1,3-indandiones are competitive inhibitors of vitamin K in the biosynthesis of prothrombin. They prevent the formation of prothrombin that contains 10 γ-carboxyglutamic acid residues that are crucial for the optimal activity of thrombin formed by the action of factor Xa.

For thrombin to be fully functional as a clotting enzyme in the presence of Ca^{+2} and phospholipids, it should possess ten γ-carboxyglutamic acid (Gla) residues in its N-terminal end. These Gla residues bind several Ca^{+2} ions under physiological conditions resulting in a specific conformation of the molecule that is important for fibrinogen recognition and cleavage activity. Under normal circumstances, ten glutamic acid (Glu) residues in prothrombin are γ-carboxylated to give a prothrombin molecule in a post-translational modification reaction that is catalyzed vitamin K (Figure 12). Thus vitamin K is required in the liver biosynthesis of the prothrombin that contains ten γ-carboxyglutamic residues. Only this prothrombin molecule containing ten Gla residues on activation with factor Xa results in a thrombin molecule that is fully functional under physiological conditions.

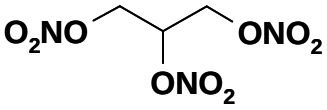
The three-dimensional structure anticoagulant coumarins and 1,3-indandiones resembles vitamin K, thus they compete for the vitamin K binding site on both vitamin K epoxide reductase and vitamin K reductase resulting in inhibition of γ-carboxylation of the Glu residues in prothrombin. Thus, an abnormal prothrombin is synthesized in the presence anticoagulant coumarins and 1,3-indandiones that when activated to thrombin has less than 2% of the proteolytic activity for fibrinogen than normal thrombin.

This inhibition of formation of Gla residues is not restricted to prothrombin alone, and is likely to occur for all zymogen forms of the enzymes of the coagulation cascade, thus enhancing the potency of the oral anticoagulants.

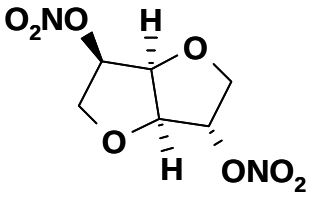
Because coumarins and 1,3-indandiones do not inactivate thrombin and factor that might be pre-formed before the administration of the oral anticoagulants, the antithrombotic effect of these molecules is not observed immediately. The observed slow onset may also be due to the time required for the body to eliminate pre-drug prothrombin blood levels (half-life ~2.5 days). The longer duration of action is because of the time required by liver to resynthesize normal prothrombin following suspension of oral anticoagulation therapy. Coumarins and 1,3-indandiones interact with certain drugs. For example, the action of oral anticoagulants can be enhanced by phenylbutazone and salicylates, while antagonized by barbiturates and vitamin K.



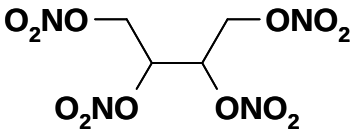
1. Amyl nitrite



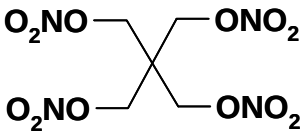
2. Glyceryl trinitrate
(nitroglycerin)



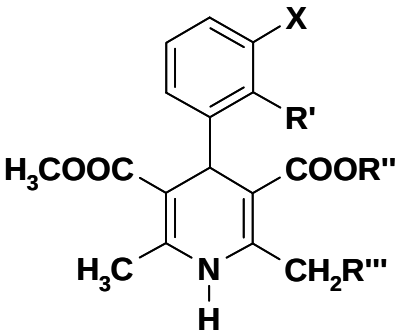
3. Isosorbide dinitrate



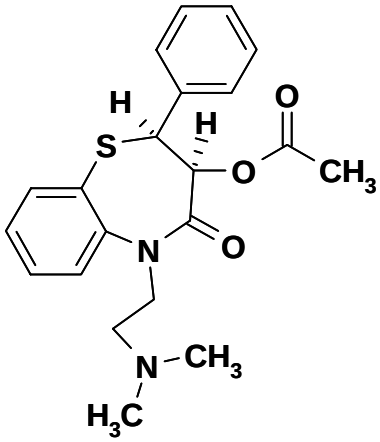
4. Erythritol tetranitrate



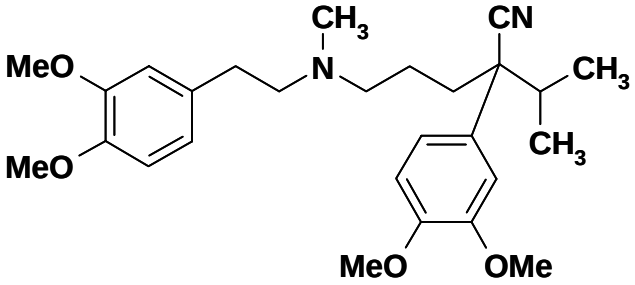
5. Pentaerythritol tetranitrate



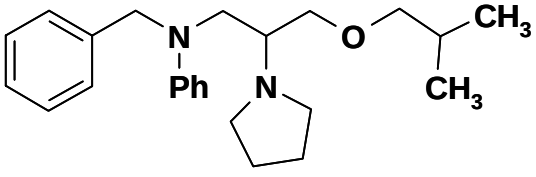
		R'	R''	R'''	X
6a.	**Nifedipine**	$-NO_2$	$-CH_3$	-H	-H
6b.	**Amlodipine**	-Cl	$-C_2H_5$	$-O-(CH_2)_2-NH_2$	-X
6c.	**Nicardipine**	-H	$-(CH_2)_2N(CH_3)(CH_2Ph)$	-H	$-NO_2$



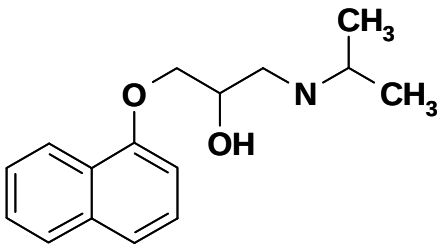
7. Diltiazem



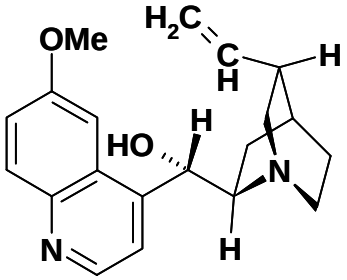
8a. Verapamil



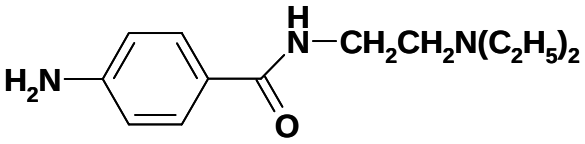
8b. Bepridil



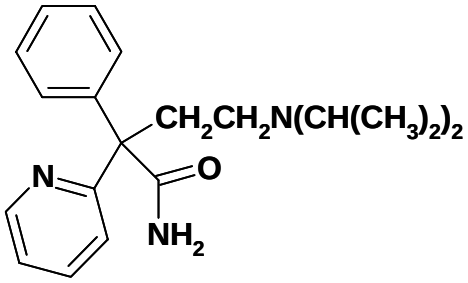
9. Propranolol



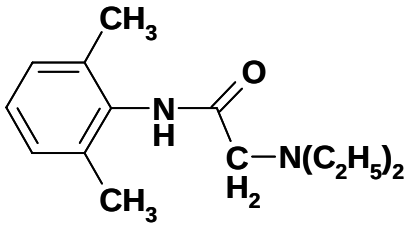
10. Quinidine



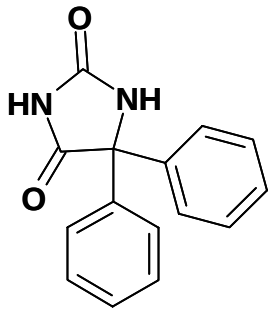
11. Procainamide



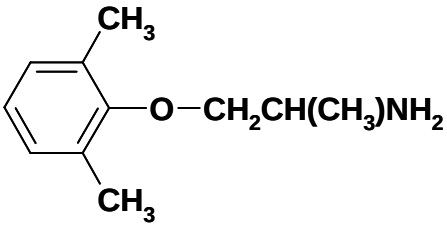
12. Disopyramide



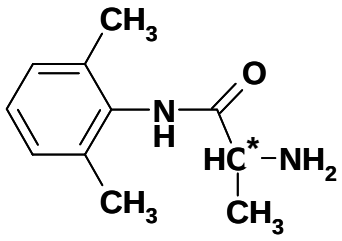
13. Lidocaine



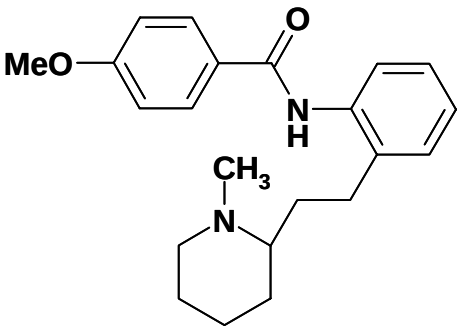
14. Phenytoin



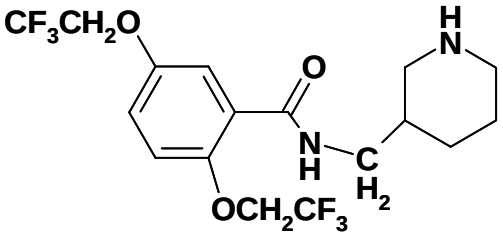
15. Mexiletine



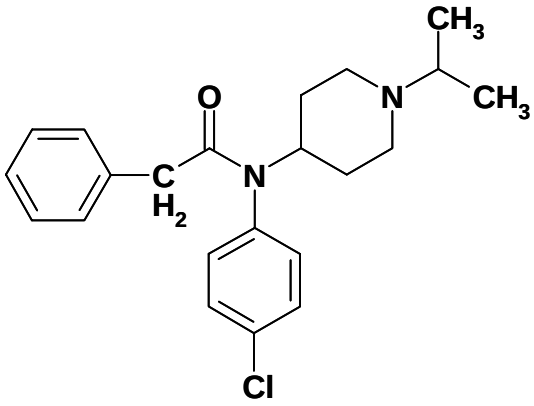
16. Tocainide



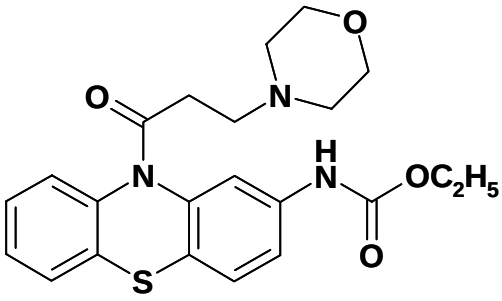
17. Encainide



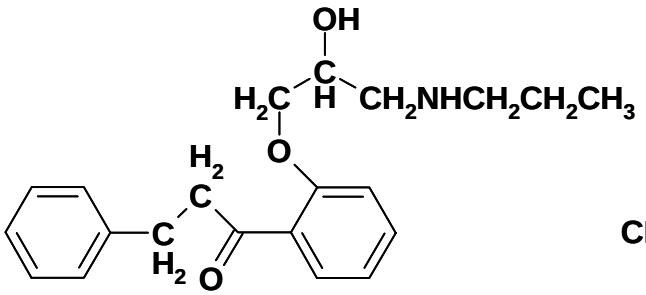
18. Flecainide



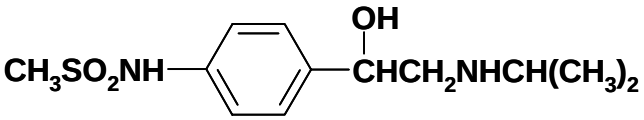
19. Lorcainide



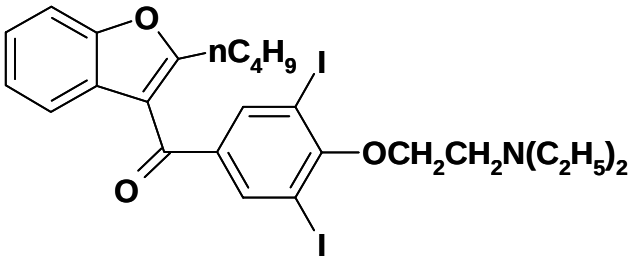
20. Morcizine



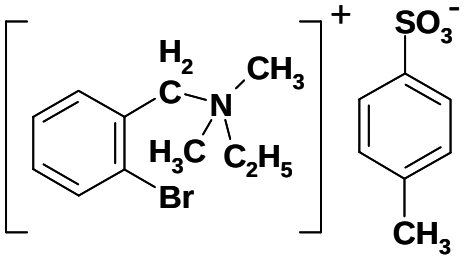
21. Propafenone



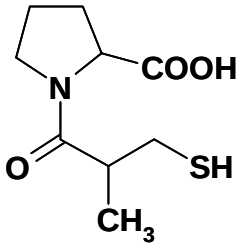
22. Sotalol



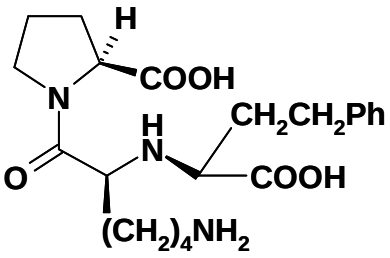
23. Amiodarone



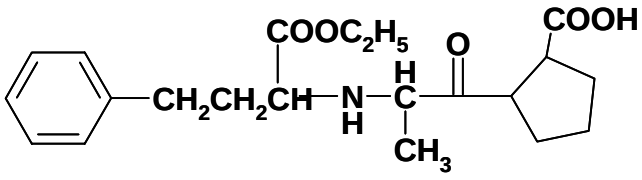
24. Bretylium tosylate



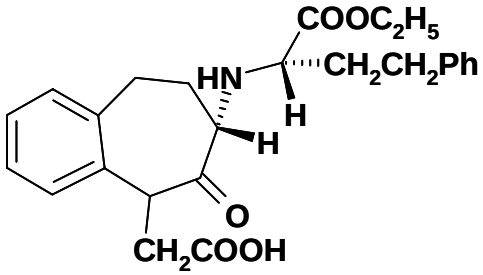
25. Captopril



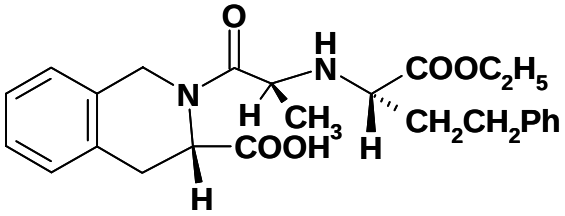
26. Lisinopril



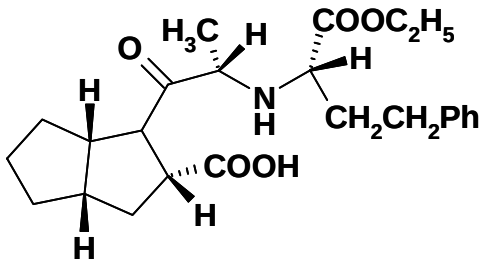
27. Enalapril



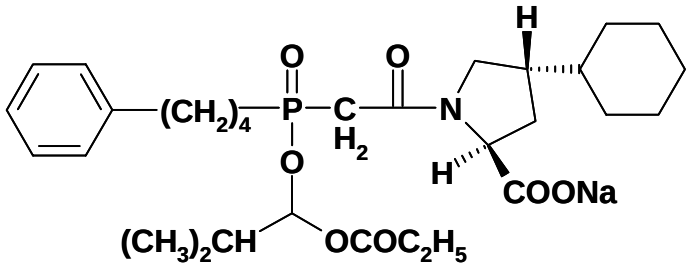
28. Benzapril

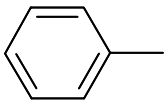


29. Quinapril

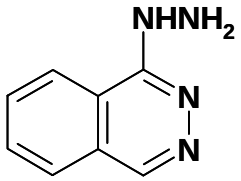


30. Ramipril





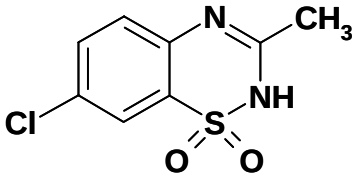
31. Fosinopril



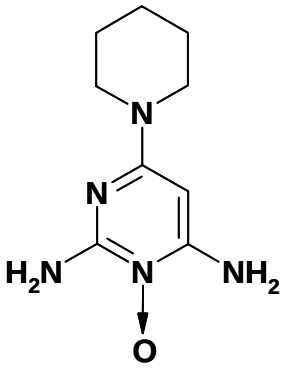
32. Hydralazine

$Na_2[Fe(CN)_5NO]$

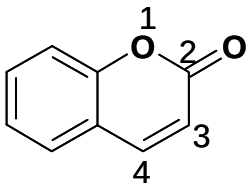
33. Sodium nitroprusside



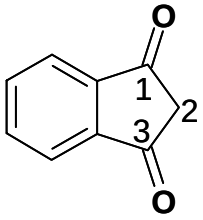
34. Diazoxide



35. Minoxidil



36. Coumarin



37. 1,3-Indandione

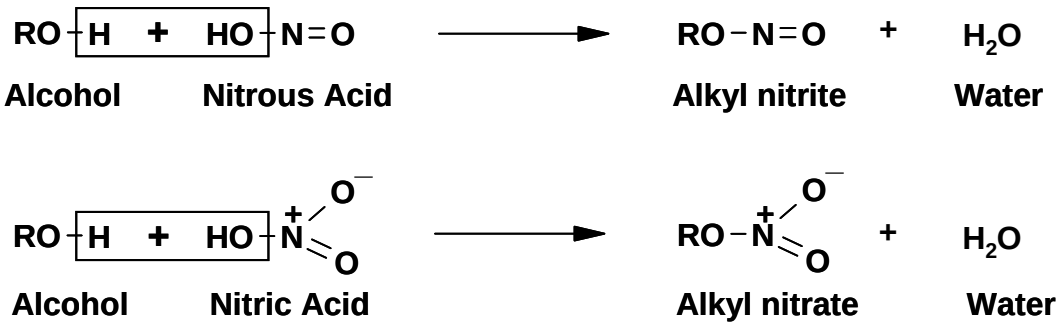


Figure 1*: Formation of alkyl nitrite or nitrate esters.*

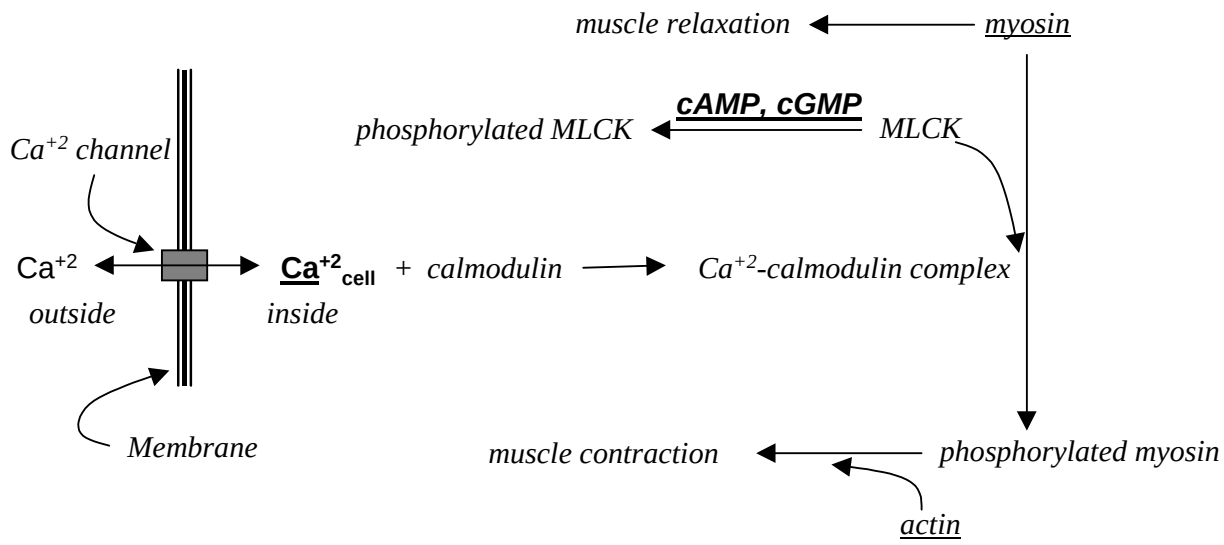


Figure 2. *Simplified biochemical mechanism of muscle contraction and relaxation. Action of cAMP or cGMP (cyclic adenine or guanosine monophosphate) results in phosphorylation of MLCK (myosin light chain kinase) that prevents myosin from being phosphorylated, thus retaining muscles in the relaxed state. See text for details.*

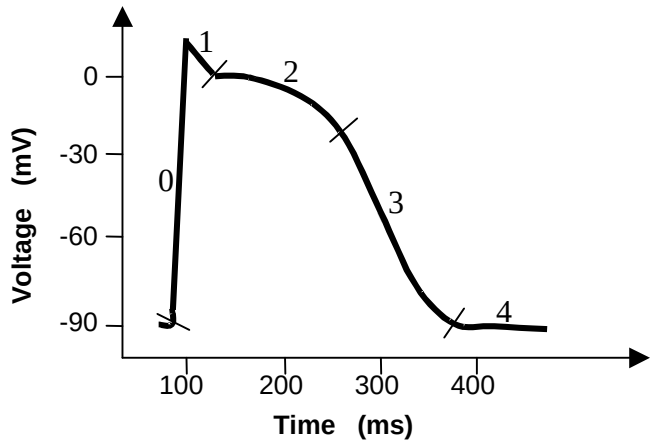


Figure 3 *A representation of the membrane action potential (upper trace) and an electrocardiogram (lower trace). Phase 0 corresponds to rapid depolarization (inward movement of* Na^{+} *ions), while phases 1 through 4 are repolarizations through movement of* K^{+}, Ca^{+2} *and* Cl^{-} *ions. Repolarization is completed during phase 4, the resting phase. The duration of action potential is the total time for 0-3 segment.*

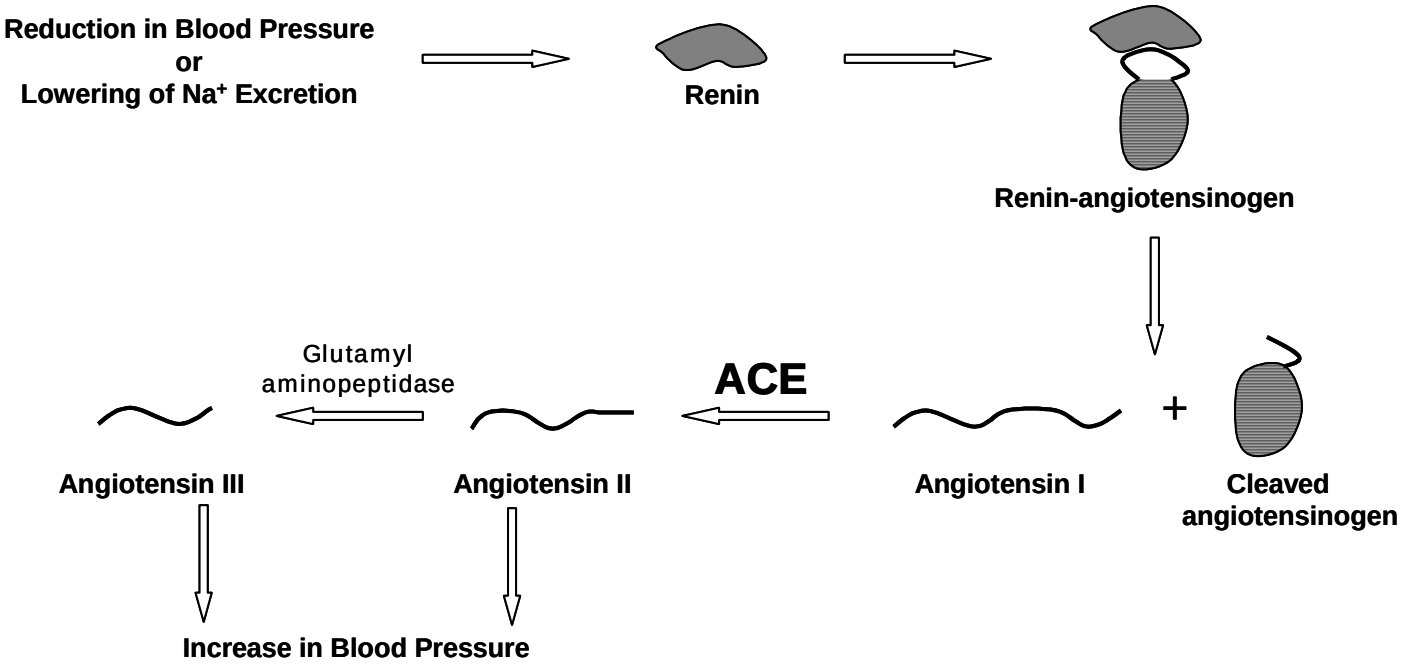


Figure 4*: The renin-angiotensin system of blood pressure control. ACE inhibitors inactivate angiotensin – converting enzyme (ACE) thereby preventing the formation of peptides angiotensin II and III, agents that mediate the signal for increasing the systemic blood pressure.*

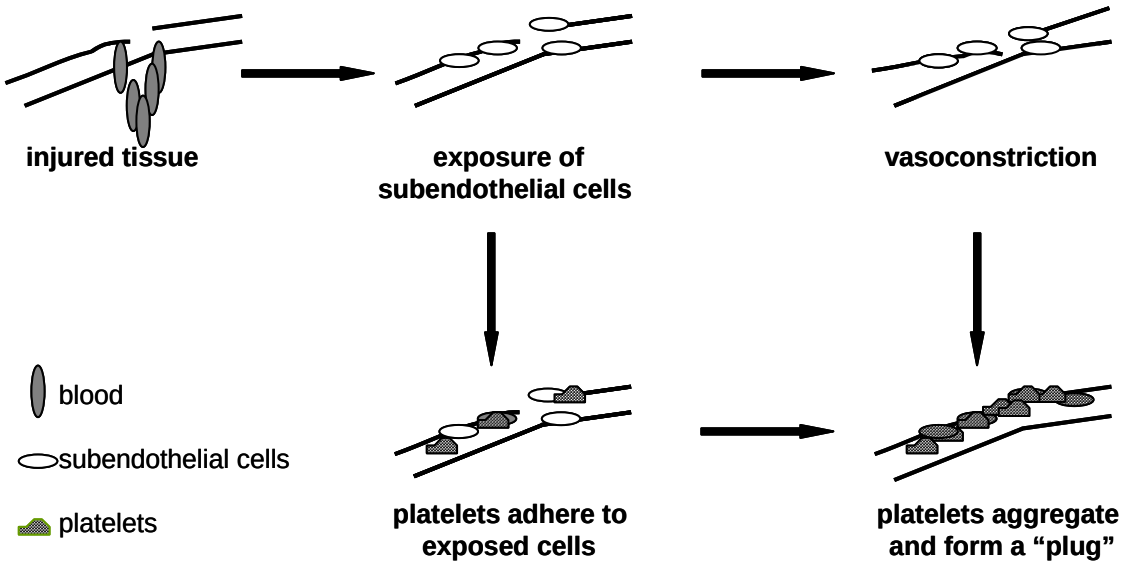


Figure 5*: Physical forces in the process of clotting.*

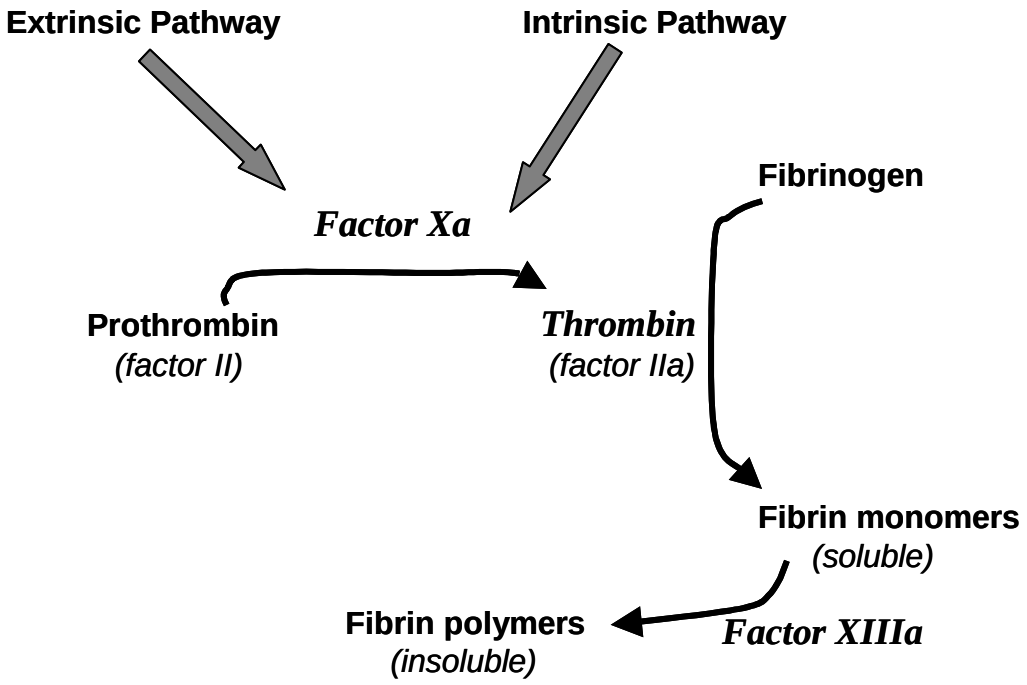


Figure 6: *A simplified representation of the formation of insoluble form of fibrin. The process of fibrin formation is enormously more complicated than that shown here and consists of many more enzymes and other species including* Ca^{+2} *ions and phospholipids.*

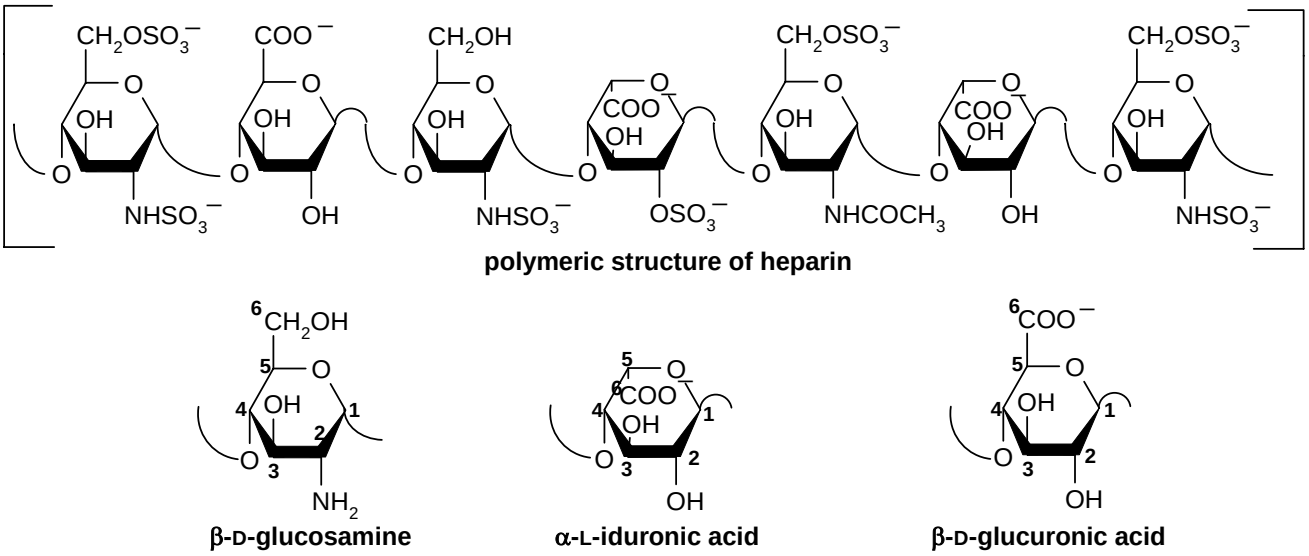


Figure 7. *Structure of full-length heparin sequence and its constituent individual monosaccharide residues.*

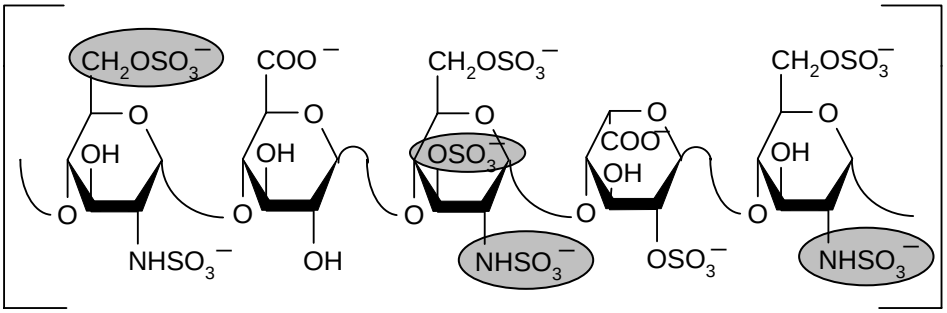


Figure 8. *Structure of the active site, pentasaccharide sequence, in full-length heparin. Negatively charged groups highlighted in ovals are critical for high-affinity binding and activation of antithrombin for accelerated inhibition of factor Xa and thrombin.*

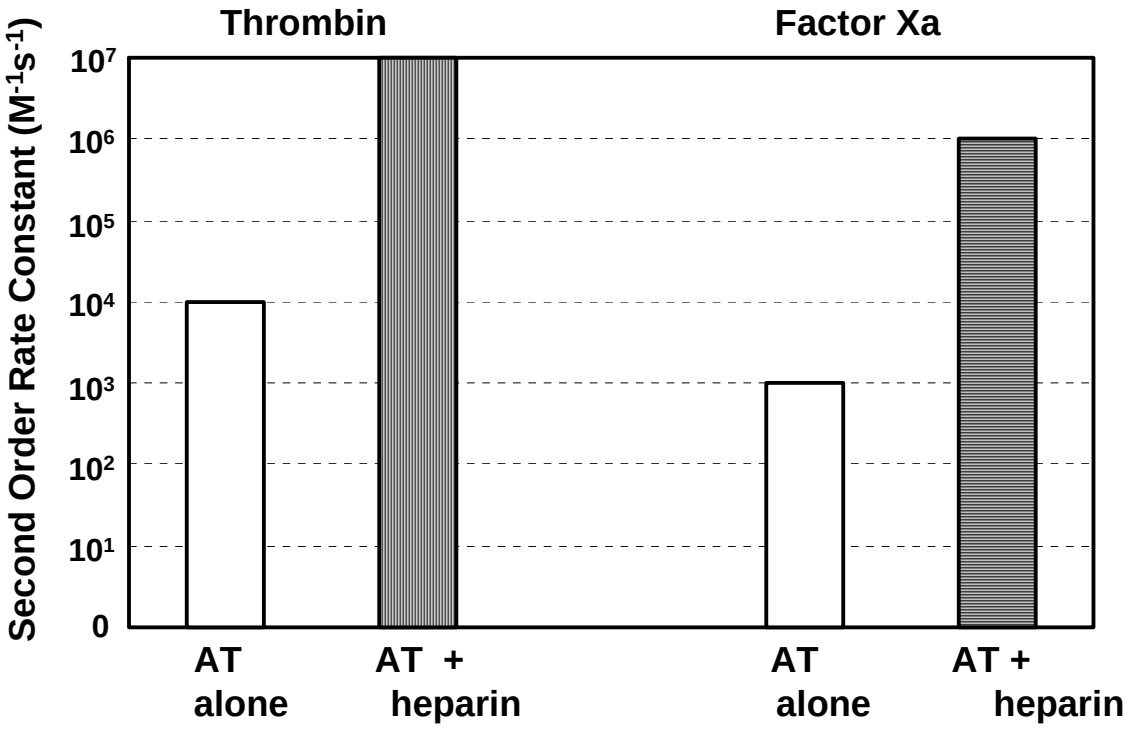


Figure 9. *Heparin accelerates the rate of antithrombin inhibition of procoagulant enzymes. The second order rate constant increase from approximately 10^3 and 10^4 for factor Xa and thrombin, respectively, with antithrombin alone to ~10^6 and 10^7 in the presence of heparin. Note the logarithmic scale on the abscissa axis. See text for details.*

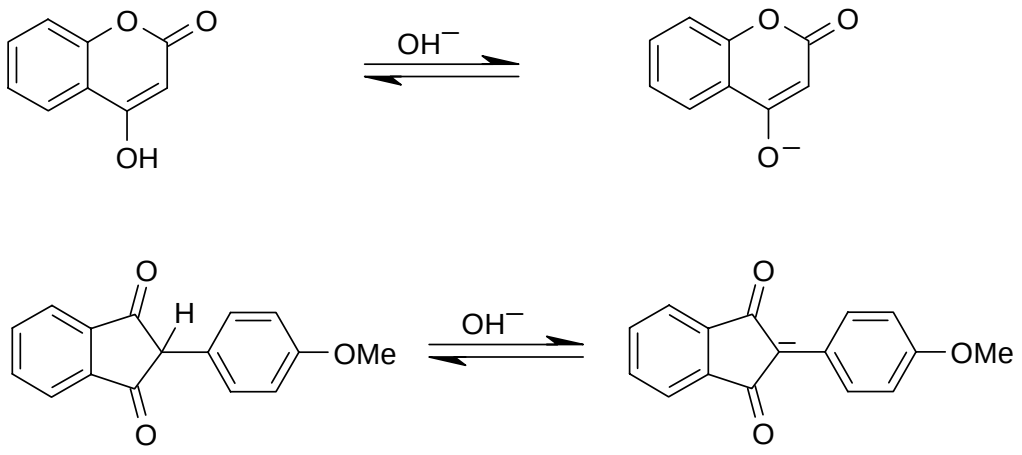
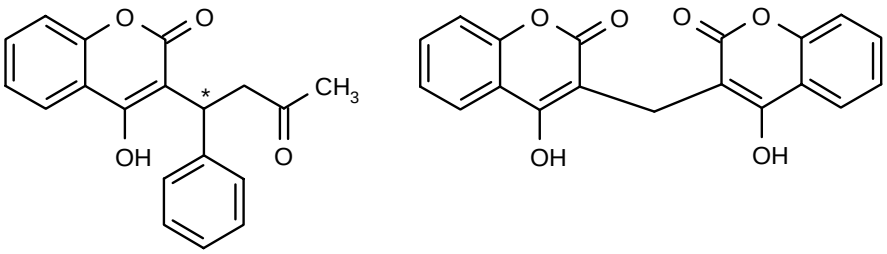
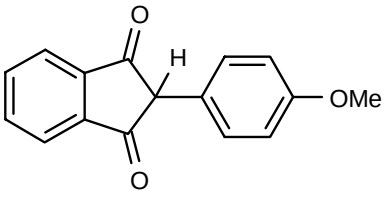


Figure 10. *Weakly acidic property of 4-hydroxy coumarins and 3-aryl-1,3-indandiones.*



warfarin
* chiral center

bishydroxycoumarin
(dicoumarol)



Anisidione
(2-(p-methoxyphenyl)-1,3--indandione

Figure 11. *Structure of clinically useful coumarins and 1,3-indandiones.*

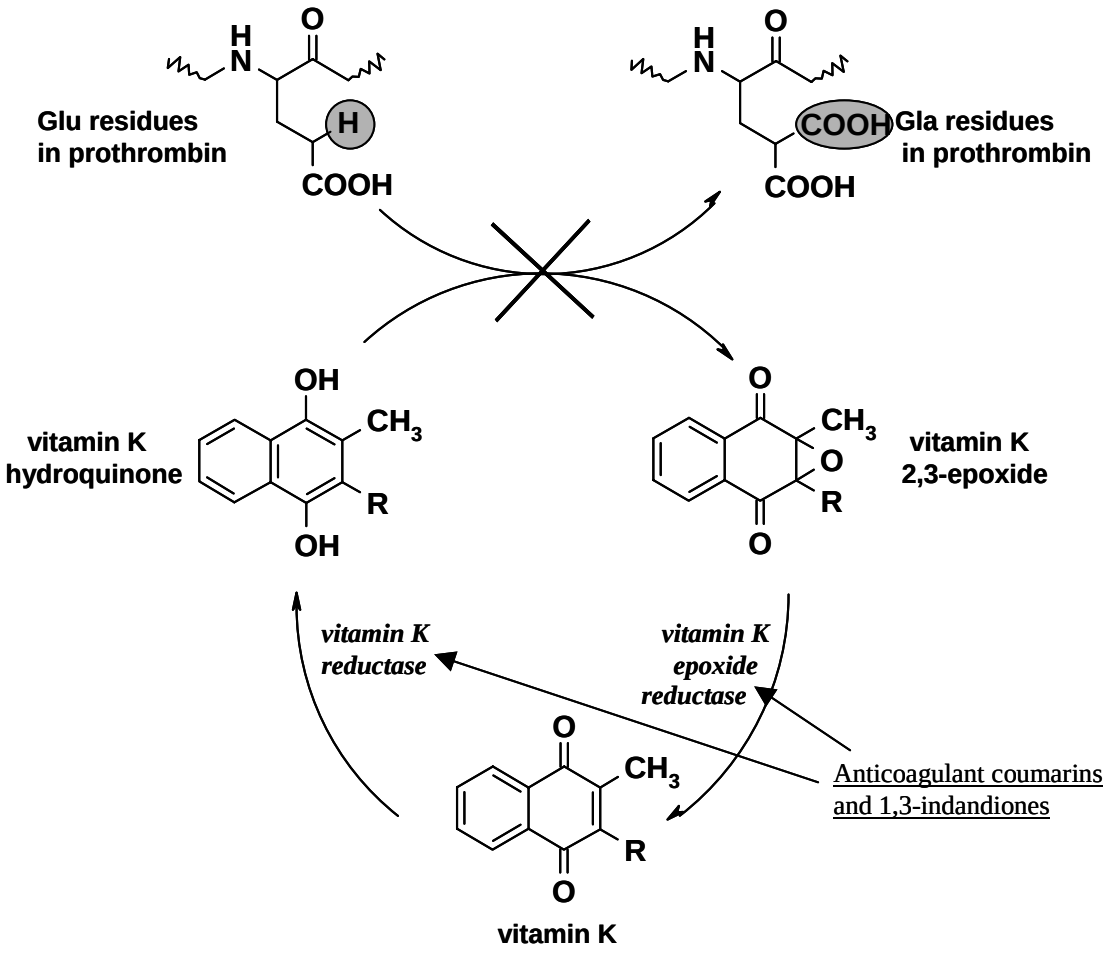


Figure 12. *: Importance of vitamin K in the γ-carboxylation of glutamic acid residues of prothrombin and inactivation of the process by anticoagulant coumarins and 1,3-indandiones. These anticoagulants inhibit vitamin K reductase and vitamin K epoxide reductase, enzymes that play an important role in the oxidation – reduction process necessary for γ-carboxylation of prothrombin. See text for details.*

Table 1: Classes of Anti-arrhythmic drugs

Class	Drugs	Mode of Action
IA	Quinidine, procainamide, disopyramide	Decreases MRD*, lengthens duration of action potential
IB	Lidocaine, phenytoin, tocainide, mexiletine	Decreases MRD, shortens duration of action potential
IC	Encainide, flecainide, lorcainide, moricizine, propafenone	Decreases MRD, no effect on the duration of action potential
II	β-adrenergic blockers (e.g., propanolol)	Suppresses adrenergic induced automaticity
III	Amiodarone, bretylium, sotalol	Many mechanisms, lengthens duration of action potential
IV	Calcium channel blockers (e.g., verapamil, diltiazem)	Inhibit slow Ca^{+2} channel, lengthen duration of action potential

*maximal rate of depolarization

Table 2: ACE Inhibitors

Drug	Absorption	Peak Action	Duration	Metabolism
Captopril	60-75%	1-2 h	6-12 h	liver
Lisinopril	25%	6-8 h	24 h	none
Enalapril	70%	4-8 h	12-24 h	Enalaprilat
Benazepril	37%	2-6 h	20-24 h	Benazeprilat
Quinapril	readily	2-4 h	~24 h	Quinaprilat
Ramipril	60%	6-8 h	~24 h	Ramiprilat
Fosinopril	readily	3 h	24 h	Fosinoprilat