**Lecture 1: CARDIOTONIC DRUGS.**

 **ANTIARRHYTHMIC DRUGS**

**CARDIOTONIC DRUGS**

Although digitalis is not the first drug and never the only drug used in heart failure, we begin our discussion with this group because other drugs used in this condition are discussed in more detail in other chapters.

**DIGITALIS**

Digitalis is the name of the genus of plants that provide most of the medically useful cardiac glycosides, eg, digoxin. Such plants have been known for thousands of years but were used erratically and with variable success until 1785, when William Withering, an English physician and botanist, published a monograph describing the clinical effects of an extract of the purple foxglove plant (*Digitalis purpurea*, a major source of these agents).

**Pharmacodynamics**

Digoxin has multiple direct and indirect cardiovascular effects, with both therapeutic and toxic consequences. In addition, it has undesirable effects on the CNS and gut. At the molecular level, all therapeutically useful cardiac glycosides inhibit Na+/K+-ATPase, the membrane-bound transporter often called the sodium pump. Although several isoforms of this ATPase occur and have varying sensitivity to cardiac glycosides, they are highly conserved in evolution. Inhibition of this transporter over most of the dose range has been extensively documented in all tissues studied. It is probable that this inhibitory action is largely responsible for the therapeutic effect (positive inotropy) as well as a major portion of the toxicity of digitalis. Other molecular-level effects of digitalis have been studied in the heart and are discussed below. The fact that a receptor for cardiac glycosides exists on the sodium pump has prompted some investigators to propose that an endogenous digitalis-like steroid, possibly ouabain or marinobufagenin, must exist. Furthermore, additional functions of Na+/K+-ATPase have been postulated, involving apoptosis, cell growth and differentiation, immunity, and carbohydrate metabolism. Indirect evidence for such endogenous digitalis-like activity has been inferred from clinical studies showing some protective effect of digoxin antibodies in preeclampsia.

**A. Cardiac Effects**

**1. Mechanical effects** — Cardiac glycosides increase contraction of the cardiac sarcomere by increasing the free calcium concentration in the vicinity of the contractile proteins during systole. The increase in calcium concentration is the result of a two-step process: first, an increase of intracellular sodium concentration because of Na+/K+-ATPase inhibition; and second, a relative reduction of calcium expulsion from the cell by the sodiumcalcium exchanger caused by the increase in intracellular sodium. The increased cytoplasmic calcium is sequestered by SERCA in the SR for later release. Other mechanisms have been proposed but are not well supported. The net result of the action of therapeutic concentrations of a cardiac glycoside is a distinctive increase in cardiac contractility. In isolated myocardial preparations, the rate of development of tension and of relaxation are both increased, with little or no change in time to peak tension. This effect occurs in both normal and failing myocardium, but in the intact patient, the responses are modified by cardiovascular reflexes and the pathophysiology of heart failure.

**2. Electrical effects** — The effects of digitalis on the electrical properties of the heart are a mixture of direct and autonomic actions. Direct actions on the membranes of cardiac cells follow a well-defined progression: an early, brief prolongation of the action potential, followed by shortening (especially the plateau phase).

The decrease in action potential duration is probably the result of increased potassium conductance that is caused by increased intracellular calcium. All these effects can be observed at therapeutic concentrations in the absence of overt toxicity. At higher concentrations, resting membrane potential is reduced (made less negative) as a result of inhibition of the sodium pump and reduced intracellular potassium. As toxicity progresses, oscillatory depolarizing afterpotentials appear following normally evoked action potentials. The afterpotentials (also known as delayed after-depolarizations, DADs) are associated with overloading of the intracellular calcium stores and oscillations in the free intracellular calcium ion concentration. When afterpotentials reach threshold, they elicit action potentials (premature depolarizations, ectopic “beats”) that are coupled to the preceding normal action potentials. If afterpotentials in the Purkinje conducting system regularly reach threshold in this way, bigeminy will be recorded on the electrocardiogram. With further intoxication, each afterpotential-evoked action potential will itself elicit a suprathreshold afterpotential, and a self-sustaining tachycardia will be established. If allowed to progress, such a tachycardia may deteriorate into fibrillation; in the case of ventricular fibrillation, the arrhythmia will be rapidly fatal unless corrected. Autonomic actions of cardiac glycosides on the heart involve both the parasympathetic and the sympathetic systems. At low therapeutic doses, cardioselective parasympathomimetic effects predominate. In fact, these atropine-blockable effects account for a significant portion of the early electrical effects of digitalis. This action involves sensitization of the baroreceptors, central vagal stimulation, and facilitation of muscarinic transmission at the nerve ending–myocyte synapse. Because cholinergic innervation is much richer in the atria, these actions affect atrial and atrioventricular nodal function more than Purkinje or ventricular function. Some of the cholinomimetic effects are useful in the treatment of certain arrhythmias. At toxic levels, sympathetic outflow is increased by digitalis. This effect is not essential for typical digitalis toxicity but sensitizes the myocardium and exaggerates all the toxic effects of the drug.

**B. Effects on Other Organs**

Cardiac glycosides affect all excitable tissues, including smooth muscle and the CNS. The gastrointestinal tract is the most common site of digitalis toxicity outside the heart. The effects include anorexia, nausea, vomiting, and diarrhea. This toxicity is caused in part by direct effects on the gastrointestinal tract and in part by CNS actions. CNS effects include vagal and chemoreceptor trigger zone stimulation. Less often, disorientation and hallucinations— especially in the elderly—and visual disturbances are noted. The latter effect may include aberrations of color perception. Gynecomastia is a rare effect reported in men taking digitalis.

**C. Interactions with Potassium, Calcium, and Magnesium**

Potassium and digitalis interact in two ways. First, they inhibit each other’s binding to Na+/K+-ATPase; therefore, hyperkalemia reduces the enzyme-inhibiting actions of cardiac glycosides, whereas hypokalemia facilitates these actions. Second, increased cardiac automaticity is inhibited by hyperkalemia. Moderately increased extracellular K+ therefore reduces the toxic effects of digitalis. Calcium ion facilitates the toxic actions of cardiac glycosides by accelerating the overloading of intracellular calcium stores that appears to be responsible for digitalis-induced abnormal automaticity. Hypercalcemia therefore increases the risk of a digitalis-induced arrhythmia. The effects of magnesium ion are opposite to those of calcium. These interactions mandate careful evaluation of serum electrolytes in patients with digitalis-induced arrhythmias.

**BIPYRIDINES**

Milrinone is a bipyridine compound that inhibits phosphodiesterase isozyme 3 (PDE-3). It is active orally as well as parenterally but is available only in parenteral form. It has an elimination half-life of 3–6 hours, with 10–40% being excreted in the urine. An older congener, inamrinone, has been withdrawn in the USA.

**Pharmacodynamics**

The bipyridines increase myocardial contractility by increasing inward calcium flux in the heart during the action potential; they may also alter the intracellular movements of calcium by influencing the SR. In addition, they have an important vasodilating effect. Inhibition of phosphodiesterase results in an increase in cAMP and the increase in contractility and vasodilation. The toxicity of inamrinone includes nausea and vomiting; arrhythmias, thrombocytopenia, and liver enzyme changes have also been reported in a significant number of patients. As noted, this drug has been withdrawn. Milrinone appears less likely to cause bone marrow and liver toxicity, but it does cause arrhythmias. Milrinone is now used only intravenously and only for acute heart failure or severe exacerbation of chronic heart failure.

**BETA-ADRENOCEPTOR AGONISTS**

The selective β1 agonist that has been most widely used in patients with heart failure is dobutamine. This parenteral drug produces an increase in cardiac output together with a decrease in ventricular filling pressure. Some tachycardia and an increase in myocardial oxygen consumption have been reported. Therefore, the potential for producing angina or arrhythmias in patients with coronary artery disease is significant, as is the tachyphylaxis that accompanies the use of any β stimulant. Intermittent dobutamine infusion may benefit some patients with chronic heart failure. Dopamine has also been used in acute heart failure and may be particularly helpful if there is a need to raise blood pressure.

**INVESTIGATIONAL POSITIVE INOTROPIC DRUGS**

Istaroxime is an investigational steroid derivative that increases contractility by inhibiting Na+/K+-ATPase (like cardiac glycosides) but in addition appears to facilitate sequestration of Ca2+ by the SR. The latter action may render the drug less arrhythmogenic than digitalis. Levosimendan, a drug that sensitizes the troponin system to calcium, also appears to inhibit phosphodiesterase and to cause some vasodilation in addition to its inotropic effects. Some clinical trials suggest that this drug may be useful in patients with heart failure, and the drug has been approved in some countries. Omecamtiv mecarbil is an investigational parenteral agent that activates cardiac myosin and prolongs systole without increasing oxygen consumption of the heart. It has been shown to reduce signs of heart failure in animal models, and a small initial phase 2 clinical trial in patients with heart failure showed increased systolic time and stroke volume and reduced heart rate and end-systolic and diastolic volumes. A larger trial in patients with acute heart failure was disappointing, but another trial in those with chronic failure is under way.

**DIURETICS**

Diuretics, especially furosemide, are drugs of choice in heart failure. They reduce salt and water retention, edema, and symptoms. They have no direct effect on cardiac contractility; their major mechanism of action in heart failure is to reduce venous pressure and ventricular preload. The reduction of cardiac size, which leads to improved pump efficiency, is of major importance in systolic failure. In heart failure associated with hypertension, the reduction in blood pressure also reduces afterload. Spironolactone and eplerenone, the aldosterone (mineralocorticoid) antagonist diuretics, have the additional benefit of decreasing morbidity and mortality in patients with severe heart failure who are also receiving ACE inhibitors and other standard therapy. One possible mechanism for this benefit lies in accumulating evidence that aldosterone may also cause myocardial and vascular fibrosis and baroreceptor dysfunction in addition to its renal effects. Finerenone is an investigational mineralocorticoid antagonist that may be less likely to induce hyperkalemia.

**ANGIOTENSIN-CONVERTING ENZYME INHIBITORS, ANGIOTENSIN RECEPTOR BLOCKERS, & RELATED AGENTS**

These versatile drugs reduce peripheral resistance and thereby reduce afterload; they also reduce salt and water retention (by reducing aldosterone secretion) and in that way reduce preload. The reduction in tissue angiotensin levels also reduces sympathetic activity through diminution of angiotensin’s presynaptic effects on norepinephrine release. Finally, these drugs reduce the long-term remodeling of the heart and vessels, an effect that may be responsible for the observed reduction in mortality and morbidity.

Angiotensin AT1 receptor blockers such as losartan appear to have similar beneficial effects. In combination with sacubitril, valsartan is now approved for HFrEF. Angiotensin receptor blockers should be considered in patients intolerant of ACE inhibitors because of incessant cough. Aliskiren, a renin inhibitor approved for hypertension, was found to have no definitive benefit in clinical trials for heart failure.

**VASODILATORS**

Vasodilators are effective in acute heart failure because they provide a reduction in preload (through venodilation), or reduction in afterload (through arteriolar dilation), or both. Some evidence suggests that long-term vasodilation by hydralazine and isosorbide dinitrate can also reduce damaging remodeling of the heart. A synthetic form of the endogenous peptide brain natriuretic peptide (BNP) is approved for use in acute (not chronic) cardiac failure as nesiritide. This recombinant product increases cGMP in smooth muscle cells and reduces venous and arteriolar tone in experimental preparations. It also causes diuresis. However, large trials with this drug have failed to show an improvement in mortality or rehospitalizations. The peptide has a short half-life of about 18 minutes and is administered as a bolus intravenous dose followed by continuous infusion. Excessive hypotension is the most common adverse effect. Reports of significant renal damage and deaths have resulted in extra warnings regarding this agent, and it should be used with great caution. A newer approach to modulation of the natriuretic peptide system is inhibition of the neutral endopeptidase enzyme, neprilysin, which is responsible for the degradation of BNP and atrial natriuretic peptide (ANP), as well as angiotensin II, bradykinin, and other peptides. Sacubitril is a prodrug that is metabolized to an active neprilysin inhibitor plus an ARB. A combination of valsartan plus sacubitril has recently been approved for use in HFrEF. Plasma concentrations of endogenous BNP rise in most patients with heart failure and are correlated with severity. Measurement of the plasma precursor NT-proBNP is a useful diagnostic or prognostic test and has been used as a surrogate marker in clinical trials. Related peptides include ANP and urodilatin, a similar peptide produced in the kidney. Carperitide and ularitide, respectively, are investigational synthetic analogs of these endogenous peptides and are in clinical trials. Bosentan and tezosentan, orally active competitive inhibitors of endothelin, have been shown to have some benefits in experimental animal models with heart failure, but results in human trials have been disappointing. Bosentan is approved for use in pulmonary hypertension. It has significant teratogenic and hepatotoxic effects. Several newer agents are thought to stabilize the RyR channel and may reduce Ca2+ leak from the SR. They are currently denoted only by code numbers. This action, if confirmed to reduce diastolic stiffness, would be especially useful in diastolic failure with preserved ejection fraction.

**BETA-ADRENOCEPTOR BLOCKERS**

Most patients with chronic heart failure respond favorably to certain β blockers despite the fact that these drugs can precipitate acute decompensation of cardiac function. Studies with bisoprolol, carvedilol, metoprolol, and nebivolol showed a reduction in mortality in patients with stable severe heart failure, but this effect was not observed with another β blocker, bucindolol. A full understanding of the beneficial action of β blockade is lacking, but suggested mechanisms include attenuation of the adverse effects of high concentrations of catecholamines (including apoptosis), up-regulation of β receptors, decreased heart rate, and reduced remodeling through inhibition of the mitogenic activity of catecholamines.

**OTHER DRUGS**

Neuroregulatory proteins appear to have cardiac and neural effects. The neuregulin GGF2 protein (cimaglermin) has been shown to benefit cardiac function in several animal models of heart failure. Drugs used in type 2 diabetes have been of concern because of the association of this condition with cardiac events. Therefore, it is of interest that some of these agents appear to benefit patients with both heart failure and type 2 diabetes. Liraglutide, a GLP-1 agonist, has been shown in some studies to nonsignificantly reduce deaths from cardiovascular causes as well as the rates of myocardial infarction, nonfatal stroke, and hospitalization for heart failure. Empagliflozin, an SGLT2 inhibitor, has also been shown to reduce hospitalizations for heart failure.

**ANTYRRHYTHMIC DRUGS**

Arrhythmias may require treatment because rhythms that are too rapid, too slow, or asynchronous can reduce cardiac output. Some arrhythmias can precipitate more serious or even lethal rhythm disturbances; for example, early premature ventricular depolarizations can precipitate ventricular fibrillation. In such patients, antiarrhythmic drugs may be lifesaving. On the other hand, the hazards of antiarrhythmic drugs—and in particular the fact that they can precipitate lethal arrhythmias in some patients—have led to a reevaluation of their relative risks and benefits. In general, treatment of asymptomatic or minimally symptomatic arrhythmias should be avoided for this reason.

**Mechanisms of Action**

Arrhythmias are caused by abnormal pacemaker activity or abnormal impulse propagation. Thus, the aim of therapy of the arrhythmias is to reduce ectopic pacemaker activity and modify conduction or refractoriness in reentry circuits to disable circus movement. The major pharmacologic mechanisms currently available for accomplishing these goals are (1) sodium channel blockade, (2) blockade of sympathetic autonomic effects in the heart, (3) prolongation of the effective refractory period, and (4) calcium channel blockade. Antiarrhythmic drugs decrease the automaticity of ectopic pacemakers more than that of the SA node. They also reduce conduction and excitability and increase the refractory period to a greater extent in depolarized tissue than in normally polarized tissue. This is accomplished chiefly by selectively blocking the sodium or calcium channels of depolarized cells. Therapeutically useful channel-blocking drugs bind readily to activated channels (ie, during phase 0) or inactivated channels (ie, during phase 2) but bind poorly or not at all to rested channels. Therefore, these drugs block electrical activity when there is a fast tachycardia (many channel activations and inactivations per unit time) or when there is significant loss of resting potential (many inactivated channels during rest). This type of drug action is often described as use-dependent or state-dependent; that is, channels that are being used frequently, or are in an inactivated state, are more susceptible to block. Channels in normal cells that become blocked by a drug during normal activation-inactivation cycles will rapidly lose the drug from the receptors during the resting portion of the cycle. Channels in myocardium that is chronically depolarized (ie, has a resting potential more positive than −75 mV) recover from block very slowly if at all. In cells with abnormal automaticity, most of these drugs reduce the phase 4 slope by blocking either sodium or calcium channels, thereby reducing the ratio of sodium (or calcium) permeability to potassium permeability. As a result, the membrane potential during phase 4 stabilizes closer to the potassium equilibrium potential. In addition, some agents may increase the threshold (make it more positive). Beta-adrenoceptor-blocking drugs indirectly reduce the phase 4 slope by blocking the positive chronotropic action of norepinephrine in the heart. In reentry arrhythmias, which depend on critically depressed conduction, most antiarrhythmic agents slow conduction further by one or both of two mechanisms:

(1) steady-state reduction in the number of available unblocked channels, which reduces the excitatory currents to a level below that required for propagation;

(2) prolongation of recovery time of the channels still able to reach the rested and available state, which increases the effective refractory period.

As a result, early extrasystoles are unable to propagate at all; later impulses propagate more slowly and are subject to bidirectional conduction block. By these mechanisms, antiarrhythmic drugs can suppress ectopic automaticity and abnormal conduction occurring in depolarized cells—rendering them electrically silent—while minimally affecting the electrical activity in normally polarized parts of the heart. However, as dosage is increased, these agents also depress conduction in normal tissue, eventually resulting in drug-induced arrhythmias. Furthermore, a drug concentration that is therapeutic (antiarrhythmic) under the initial circumstances of treatment may become “proarrhythmic” (arrhythmogenic) during fast heart rates (more development of block), acidosis (slower recovery from block for most drugs), hyperkalemia, or ischemia.

**SPECIFIC ANTIARRHYTHMIC AGENTS**

The most widely used scheme for the classification of antiarrhythmic drug actions recognizes four classes:

1. Class 1 action is sodium channel blockade. Subclasses of this action reflect effects on the action potential duration (APD) and the kinetics of sodium channel blockade. Drugs with class 1A action prolong the APD and dissociate from the channel with intermediate kinetics; drugs with class 1B action shorten the APD in some tissues of the heart and dissociate from the channel with rapid kinetics; and drugs with class 1C action have minimal effects on the APD and dissociate from the channel with slow kinetics.

2. Class 2 action is sympatholytic. Drugs with this action reduce β-adrenergic activity in the heart.

3. Class 3 action manifests as prolongation of the APD. Most drugs with this action block the rapid component of the delayed rectifier potassium current, IKr.

4. Class 4 action is blockade of the cardiac calcium current. This action slows conduction in regions where the action potential upstroke is calcium dependent, eg, the SA and AV nodes.

A given drug may have multiple classes of action as indicated by its membrane and ECG effects. For example, amiodarone shares all four classes of action. Drugs are usually discussed according to the predominant class of action. Certain antiarrhythmic agents, eg, adenosine and magnesium, do not fit readily into this scheme and are described separately.

**SODIUM CHANNEL-BLOCKING DRUGS (CLASS 1)**

Drugs with local anesthetic action block sodium channels and reduce the sodium current, INa. They are the oldest group of antiarrhythmic drugs and are still widely used.

**Procainamide (Subgroup 1A)**

By blocking sodium channels, procainamide slows the upstroke of the action potential, slows conduction, and prolongs the QRS duration of the ECG. The drug also prolongs the APD (a class 3 action) by nonspecific blockade of potassium channels. The drug may be somewhat less effective than quinidine in suppressing abnormal ectopic pacemaker activity but more effective in blocking sodium channels in depolarized cells. Procainamide has direct depressant actions on SA and AV nodes, and these actions are only slightly counterbalanced by drug-induced vagal block.

**Quinidine (Subgroup 1A)**

Quinidine has actions similar to those of procainamide: it slows the upstroke of the action potential, slows conduction, and prolongs the QRS duration of the ECG, by blockade of sodium channels. The drug also prolongs the action potential duration by blockade of several potassium channels. Its toxic cardiac effects include excessive QT-interval prolongation and induction of torsades de pointes arrhythmia. Toxic concentrations of quinidine also produce excessive sodium channel blockade with slowed conduction throughout the heart. It also has modest antimuscarinic actions in the heart.

**Disopyramide (Subgroup 1A)**

The effects of disopyramide are very similar to those of procainamide and quinidine. Its cardiac antimuscarinic effects are even more marked than those of quinidine. Therefore, a drug that slows AV conduction should be administered with disopyramide when treating atrial flutter or fibrillation.

**Lidocaine (Subgroup 1B)**

Lidocaine has a low incidence of toxicity and a high degree of effectiveness in arrhythmias associated with acute myocardial infarction. It is used only by the intravenous route.

Lidocaine blocks activated and inactivated sodium channels with rapid kinetics; the inactivated state block ensures greater effects on cells with long action potentials such as Purkinje and ventricular cells, compared with atrial cells. The rapid kinetics at normal resting potentials result in recovery from block between action potentials and no effect on conduction. In depolarized cells, the increased inactivation and slower unbinding kinetics result in the selective depression of conduction. Little effect is seen on the ECG in normal sinus rhythm.

**Mexiletine (Subgroup 1B)**

Mexiletine is an orally active congener of lidocaine. Its electrophysiologic and antiarrhythmic actions are similar to those of lidocaine. (The anticonvulsant phenytoin exerts similar electrophysiologic effects and has been used as an antiarrhythmic.) Mexiletine is used in the treatment of ventricular arrhythmias. The elimination half-life is 8–20 hours and permits administration two or three times per day. The usual daily dosage of mexiletine is 600–1200 mg/d. Dose-related adverse effects are seen frequently at therapeutic dosage. These are predominantly neurologic, including tremor, blurred vision, and lethargy. Nausea is also a common effect.

**Flecainide (Subgroup 1C)**

Flecainide is a potent blocker of sodium and potassium channels with slow unblocking kinetics. (Note that although it does block certain potassium channels, it does not prolong the action potential or the QT interval.) It is currently used for patients with otherwise normal hearts who have supraventricular arrhythmias. It has no antimuscarinic effects.

**Propafenone (Subgroup 1C)**

Propafenone has some structural similarities to propranolol and possesses weak β-blocking activity. Its spectrum of action is very similar to that of quinidine, but it does not prolong the action potential. Its sodium channel-blocking kinetics are similar to those of flecainide. Propafenone is metabolized in the liver, with an average half-life of 5–7 hours. The usual daily dosage of propafenone is 450–900 mg/d in three divided doses. The drug is used primarily for supraventricular arrhythmias. The most common adverse effects are a metallic taste and constipation; arrhythmia exacerbation can also occur.

**BETA-ADRENOCEPTOR-BLOCKING DRUGS (CLASS 2)**

Propranolol and similar drugs have antiarrhythmic properties by virtue of their β-receptor-blocking action and direct membrane effects. Some of these drugs have selectivity for cardiac β1 receptors, some have intrinsic sympathomimetic activity, some have marked direct membrane effects, and some prolong the cardiac action potential. The relative contributions of the β-blocking and direct membrane effects to the antiarrhythmic effects of these drugs are not fully known. Although β blockers are fairly well tolerated, their efficacy for suppression of ventricular ectopic depolarizations is lower than that of sodium channel blockers. However, there is good evidence that these agents can prevent recurrent infarction and sudden death in patients recovering from acute myocardial infarction. Esmolol is a short-acting β blocker used primarily as an antiarrhythmic drug for intraoperative and other acute arrhythmias. Sotalol is a nonselective β-blocking drug that prolongs the action potential (class 3 action).

**Amiodarone**

Amiodarone is approved for oral and intravenous use to treat serious ventricular arrhythmias. However, the drug is also highly effective in the treatment of supraventricular arrhythmias such as atrial fibrillation. As a result of its broad spectrum of antiarrhythmic action, it is very extensively used for a wide variety of arrhythmias. Amiodarone has unusual pharmacokinetics and important extracardiac adverse effects. Dronedarone, an analog that lacks iodine atoms, has US Food and Drug Administration (FDA) approval for the treatment of atrial flutter and fibrillation. Celivarone is another noniodinated benzofuran derivative similar to dronedarone that is currently undergoing clinical trials for the prevention of ventricular tachycardia recurrence.

Amiodarone markedly prolongs the action potential duration (and the QT interval on the ECG) by blockade of IKr. During chronic administration, IKs is also blocked. The action potential duration is prolonged uniformly over a wide range of heart rates; that is, the drug does not have reverse use-dependent action. Despite its present classification as a class 3 agent, amiodarone also significantly blocks inactivated sodium channels. Its action potentialprolonging action reinforces this effect. Amiodarone also has weak adrenergic and calcium channel-blocking actions. Consequences of these actions include slowing of the heart rate and AV node conduction. The broad spectrum of actions may account for its relatively high efficacy and its low incidence of torsades de pointes despite significant QT-interval prolongation.

**Sotalol**

Sotalol has both β-adrenergic receptor-blocking (class 2) and action potential-prolonging (class 3) actions. The drug is formulated as a racemic mixture of d- and l-sotalol. All the β-adrenergic-blocking activity resides in the l-isomer; the d- and l-isomers share action potential prolonging effects. Beta-adrenergic-blocking action is not cardioselective and is maximal at doses below those required for action potential prolongation.

**Dofetilide**

Dofetilide has class 3 action potential prolonging action. This action is effected by a dose-dependent blockade of the rapid component of the delayed rectifier potassium current (IKr) and the blockade of IKr increases in hypokalemia. Dofetilide produces no relevant blockade of the other potassium channels or the sodium channel. Because of the slow rate of recovery from blockade, the extent of blockade shows little dependence on stimulation frequency. However, dofetilide does show less action potential prolongation at rapid rates because of the increased importance of other potassium channels such as IKs at higher frequencies.

**Verapamil**

Cardiac Effects Verapamil blocks both activated and inactivated L-type calcium channels. Thus, its effect is more marked in tissues that fire frequently, those that are less completely polarized at rest, and those in which activation depends exclusively on the calcium current, such as the SA and AV nodes. AV nodal conduction time and effective refractory period are consistently prolonged by therapeutic concentrations. Verapamil usually slows the SA node by its direct action, but its hypotensive action may occasionally result in a small reflex increase of SA rate. Verapamil can suppress both early and delayed afterdepolarizations and may abolish slow responses arising in severely depolarized tissue.

**Adenosine**

Mechanism & Clinical Use Adenosine is a nucleoside that occurs naturally throughout the body. Its half-life in the blood is less than 10 seconds. Its cardiac mechanism of action involves activation of an inward rectifier K+ current and inhibition of calcium current. The results of these actions are marked hyperpolarization and suppression of calcium-dependent action potentials. When given as a bolus dose, adenosine directly inhibits AV nodal conduction and increases the AV nodal refractory period but has lesser effects on the SA node. Adenosine is currently the drug of choice for prompt conversion of paroxysmal supraventricular tachycardia to sinus rhythm because of its high efficacy (90–95%) and very short duration of action. It is usually given in a bolus dose of 6 mg followed, if necessary, by a dose of 12 mg. An uncommon variant of ventricular tachycardia is adenosine-sensitive. The drug is less effective in the presence of adenosine receptor blockers such as theophylline or caffeine, and its effects are potentiated by adenosine uptake inhibitors such as dipyridamole.