16 Antiarrhythmic Drugs

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DRUG LIST

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Cardiac arrhythmias result from alterations in the orderly sequence of depolarization followed by repolarization in the heart. Cardiac arrhythmias may result in alterations in heart rate or rhythm and arise from alterations in impulse generation or conduction. The clinical implications of disordered cardiac activation range from asymptomatic palpitations to lethal arrhythmia.

Pharmacological management of arrhythmias uses drugs that exert effects directly on cardiac cells by inhibiting the function of specific ion channels or by altering the autonomic input into the heart. Recent technological advances have lead to an increase in nondrug strategies, including transcatheter radiofrequency ablation, intraoperative cryoablation, implanted pacemakers, and defibrillation. Physicians caring for patients with arrhythmias therefore must understand and appreciate the benefits and risks provided by each therapeutic modality, what the indication for each is, and how these modalities may interact.

Successful antiarrhythmic drug therapy requires a combination of understanding the pathophysiology of the arrhythmia, identification of a drug that can influence the relevant electrophysiological parameters, and careful titration of the drug's dose to correct the abnormal electrophysiological events giving rise to the arrhythmia. This is accomplished while avoiding the omnipresent risk of side effects such as proarrhythmia.

This chapter first provides a brief overview of the cellular events that underlie the cardiac action potential and lead to the formation and propagation of the

normal cardiac impulse. Basic mechanisms of arrhythmias are reviewed, and the pharmacology of specific antiarrhythmic agents is discussed.

CARDIAC ELECTROPHYSIOLOGY

Transmembrane Potential

Figure 16.1 shows the phases of the cardiac action potential recorded with an intracellular microelectrode. The characteristic action potential is the result of activation and inactivation of multiple ion channels, which allows the flow of charged ions across the sarcolemmal membrane. The ion channels are transmembrane proteins possessing two important features: an ion selective pore that allows the passage of a specific cation or anion and regulatory components that respond to chemical stimulation or changes in the transmembrane potential by opening or closing. The ions flow through open channels according to the electrochemical driving forces at any given moment.

Like all other electrically active cells, the interior of the cardiac muscle cell is electrically negative with respect to the surrounding medium. This difference between the exterior and interior of a myocardial cell results from the action of several energy-requiring pumps, such as the Na^+–K^+–ATPase, which pumps Na^+ out of and K^+ into the cell in a ratio of $3Na^+$ to $2K^+$, and the presence of large negatively charged intracellular proteins that do not diffuse freely across the sarcolemmal membrane. The normal resting $[K^+]_i$ is 140 mM, whereas the extracellular K^+ concentration, $[K^+]_0$, is 4 mM. The resting myocardial cell tends to be highly permeable to K^+ and less so to Na^+ and Ca^{++}; therefore, a net diffusion of K^+ flows out of the cell, leaving behind negatively charged proteins. As a result, the interior of the cell becomes electronegative, and two opposing forces are established: a chemical force due to a concentration gradient and a counteracting electrostatic force established by the negatively charged ions within the cell.

At equilibrium, the chemical and electrostatic forces are equal, and there is no net flow of ions across the

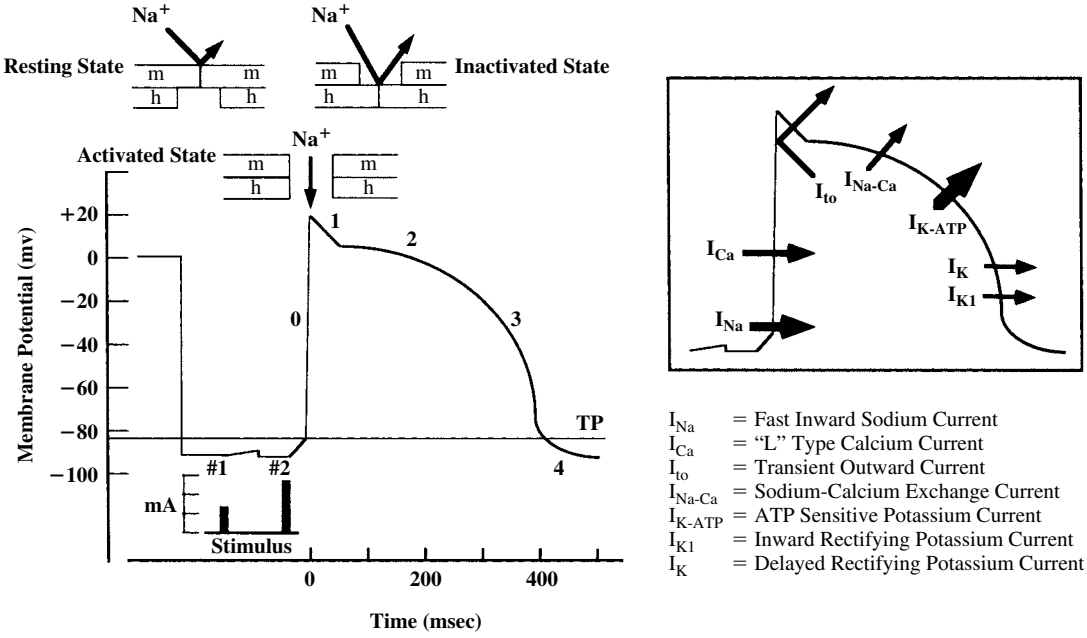

FIGURE 16.1

Transmembrane action potential of a Purkinje fiber as recorded with an intracellular microelectrode. When the electrode tip penetrates the fiber, a resting membrane potential of −90 mV is recorded. The application of a subthreshold stimulus (#1) produces a depolarizing current that fails to result in excitation of the myocardial cell. The application of a threshold stimulus (#2) reaches the threshold potential (TP) and results in an inward current and an action potential. Major transmembrane currents carried by specific ions entering the cell through selective ion channels are depicted to the right. Antiarrhythmic agents alter the electrophysiologic properties of the cardiac cells by modulating one or more of the transmembrane currents, especially the fast inward sodium current and the transmembrane currents carried by the potassium ion (I_K and $I_{K\text{-}ATP}$). I_{NA} = fast inward sodium current; I_{CA} = "L"-type calcium current; I_{to} = transient outward current; $I_{Na\text{-}Ca}$ = sodium-calcium exchange current; $I_{K\text{-}ATP}$ = adenosine triphosphate-sensitive potassium current; I_K = inward rectifying potassium current; I_K = delayed rectifying potassium current.

sarcolemmal membrane. The membrane potential at which this occurs may be calculated using the Nernst equation:

$$E_x = -61 \log([x]_i/[x]_o)$$

In this equation, x is the ion in question, $[x]_i$ is the concentration inside the cell, and $[x]_o$ is the concentration outside the cell. For potassium, using a $[K]_i$ of 140 mM and a $[K]_o$ of 4 mM, the E_K is equal to –94 mV, which is almost identical to the normal resting membrane potential of −90 mV. The contribution of other ionic species to the resting membrane potential is smaller because of the low transmembrane permeability at hyperpolarized resting membrane potentials.

An examination of the relationship of $[K^+]_o$] and $[K^+]_i$] in the Nernst equation shows that an increase in the $[K^+]_o$ will result in a decrease in the membrane resting potential (less negative). Changes in the extracellular concentration of another ion (Na^+, Ca^{++}, Mg^{++}, Cl^-) may also modify the resting potential.

To produce membrane depolarization, a current stimulus of sufficient intensity to exceed the outward K^+ current must be applied to the cell. If the depolarizing stimulus raises the membrane potential above a threshold value, sodium channels within the sarcolemmal membrane change their conformation and open their ion-selective pore, allowing Na^+ to enter the cell driven by the electrochemical gradient. The open sodium channels raise the membrane potential toward the equilibrium potential of sodium (+65 mV) and set into motion the intricate and precisely coordinated series of ion channel openings and closings leading to the characteristic action potential.

The action potential has been divided into five phases, rapid depolarization (phase 0), early repolarization (phase 1), plateau (phase 2), rapid repolarization (phase 3) and finally the resting phase in myocytes or slow diastolic depolarization (phase 4). The last is a property in cells with the potential for automaticity (defined later). A brief outline of each of these phases in the normal myocyte is given next.

Ionic Basis for the Membrane Action Potential

Phase 0: Rapid Depolarization

Phase 0 of the action potential encompasses the rapid depolarization of the myocyte induced principally by the opening of voltage gated sodium channels. The sodium channels open rapidly in response to membrane depolarization and close within 1 to 2 milliseconds in a time-dependent fashion. The conformation of the channels changes, and they enter an inactivated state in which they cannot be recruited to participate in generating a subsequent action potential for a defined interval. The interval during which the myocyte cannot be stimulated is the *absolute refractory period.* After the myocyte returns to a hyperpolarized resting potential, the channels cycle through the inactivated state back to the rested or closed conformation and again are available to open in response to a stimulus of sufficient intensity. The rate of recovery of the Na^+ channels from voltage-dependent inactivation is one determinant of the cell's ability to generate a subsequent action potential. The refractory period defines the maximal rate at which the cardiac cells will respond to applied stimuli and propagate impulses to neighboring cells. The density of available sodium channels in the cell membrane also determines the rate at which an impulse is conducted from one cell to another. The maximal upstroke velocity of phase 0 (V_{max}) is a major determinant of the speed of impulse conduction within the myocardium and therefore is important in initiation and maintenance of arrhythmia. Genetic mutations in the sodium channel resulting in a sustained inward leak current have been identified and underlie one form of the long QT syndrome (LQTS 3).

Phase 1

At the peak of the action potential upstroke, a short rapid period of repolarization occurs and the membrane potential returns toward 0 mV. This produces a spike and dome configuration of the action potential and is a result of the inactivation of the I_{Na} and activation of a short-lived outward current called the transient outward current (I_{to}). I_{to} is composed of two distinct channels carried by either potassium or chloride. The distribution of I_{to} is heterogeneous throughout the myocardium and varies from species to species. I_{to} is present in both the atrium and the ventricular myocardium. Within the ventricle, I_{to} is present in the epicardium and absent in the endocardium. Consequently, the epicardium repolarizes more rapidly than the endocardium; this is the basis for the QRS complex and the T-wave on the surface electrocardiogram having an identical axis as opposed to an opposite axis. Abnormalities in the function of I_{to} have been implicated in Brugada syndrome, a potentially lethal genetic disease resulting in ventricular tachycardia and fibrillation.

Phase 2: Action Potential Plateau

Phase 2 is characterized by a net balance between inward (depolarizing) and outward (repolarizing) ion currents maintaining the myocyte in a depolarized state. During this phase, Ca^{++} enters the cell, causing Ca^{++} release from intracellular stores and linking electrical depolarization with mechanical contraction. Interestingly, the current flow during the plateau phase is small, and therefore, perturbations in any of the currents participating in this phase (either through genetic mutations

or pharmacologically) may result in profound alterations in the action potential. Ca^{++} enters the cell through voltage-dependent channels highly selective for Ca^{++} that open when the membrane is depolarized above −40 mV. The channel (L-type calcium channel) possesses slow inactivation kinetics resulting in a long-lasting current.

Outward repolarizing K^+ currents oppose the effect of the inward $I_{Ca}{}^{++}$ on the plateau phase. This current is carried predominantly through delayed rectifier potassium channels (I_K). These channels are voltage sensitive, with slow inactivation kinetics. Three distinct subpopulations of I_K with differing activation and inactivation kinetics have been described. A rapidly activating subset (I_{Kr}), a slowly inactivating subset (I_{Ks}), and an ultra–rapidly activating subset to date are identified only in atrial tissue (I_{Kur}).

Phase 3: Late Phase of Repolarization

Termination of phase 2 of the action potential plateau occurs when time-dependent, voltage-dependent, and intracellular Ca^{++}–dependent inactivation of $I_{Ca}{}^{++}$ results in the unopposed repolarizing effects of the outward K^+ currents. The combination of these effects results in rapid repolarization with a return to the hyperpolarized resting membrane potential. Pharmacological interventions that inhibit I_K prolong the membrane action potential by delaying repolarization. Mutations in the genes encoding the various subtypes of I_K inhibit proper channel function and result in the LQTS.

Phase 4

In normal atrial and ventricular myocytes, phase 4 is electrically stable, with the resting membrane potential held at approximately −90 mV and maintained by the outward potassium leak current and ion exchangers previously described. It is during phase 4 that the Na^+ channels necessary for atrial and ventricular myocyte depolarization recover completely from inactivation. In myocytes capable of automaticity, the membrane potential slowly depolarizes during this period to initiate an action potential (discussed later).

Automaticity

Automaticity can be defined as the ability of a cell to alter its resting membrane potential toward the excitation threshold without the influence of an external stimulus. The characteristic feature of cells with automaticity is a slow decrease in the membrane potential during diastole (phase 4) such that the membrane potential reaches threshold (Figure 16.2). During phase 4 in these pacemaker cells, the background potassium leak current decreases and an inward depolarizing current (I_f) is

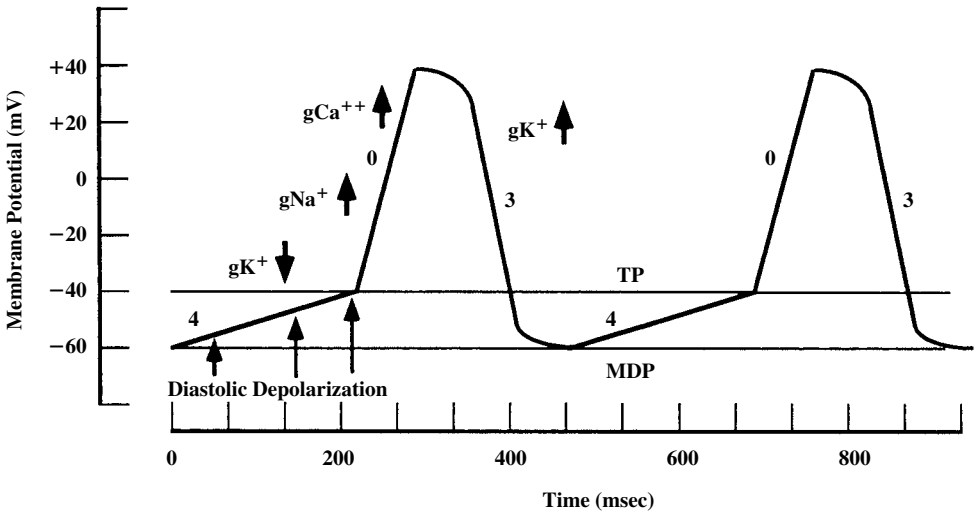

FIGURE 16.2

Transmembrane action potential of a sinoatrial node cell. In contrast to other cardiac cells, there is no phase 2 or plateau. The *threshold potential* (*TP*) is −40 mV. The maximum diastolic potential (MDP) is achieved as a result of a gradual decline in the potassium conductance (gK^+). Spontaneous phase 4 or diastolic depolarization permits the cell to achieve the TP, thereby initiating an action potential (g = transmembrane ion conductance). Stimulation of pacemaker cells within the sinoatrial node decreases the time required to achieve the TP, whereas vagal stimulation and the release of acetylcholine decrease the slope of diastolic depolarization. Thus, the positive and negative chronotropic actions of sympathetic and parasympathetic nerve stimulation can be attributed to the effects of the respective neurotransmitters on ion conductance in pacemaker cells of the sinuatrial node. gNa^+ = Na^+ conductance.

activated. In combination, this results in slow depolarization of the myocyte. If the membrane potential depolarizes above the threshold for the opening of I_{Ca}^{++}, an action potential is generated.

Myocytes within the sinoatrial node possess the most rapid intrinsic rate of automaticity; therefore, the sinoatrial node serves as the normal pacemaker of the heart. Specialized cells within the atria, atrioventricular (A-V) node, and His-Purkinje system are capable of spontaneous depolarization, albeit at a slower rate. *The more rapid rate of depolarization of the sinoatrial nodal cells normally suppresses all of the other cells with the potential for automaticity.* The other cells will become pacemakers when their own intrinsic rate of depolarization becomes greater than that of the sinoatrial node or when the pacemaker cells within the sinoatrial node are depressed. When impulses fail to conduct across the A-V node to excite the ventricular myocardium (heart block), spontaneous depolarization within the His-Purkinje system may become the dominant pacemaker maintaining cardiac rhythm and cardiac output.

The rate of pacemaker discharge within these specialized myocytes is influenced by the activity of both divisions of the autonomic nervous system. Increased sympathetic nerve activity to the heart, the release of catecholamines from the adrenal medulla, or the exogenous administration of adrenomimetic amines will cause an increase in the rate of pacemaker activity through stimulation of β-adrenoceptors on the pacemaker cells (Figure 16.3).

The parasympathetic nervous system, through the vagus nerve, inhibits the spontaneous rate of depolarization of pacemaker cells. The release of acetylcholine from cholinergic vagal fibers increases potassium conductance (gK^+) in pacemaker cells, and this enhanced outward movement of K^+ results in a more negative po-

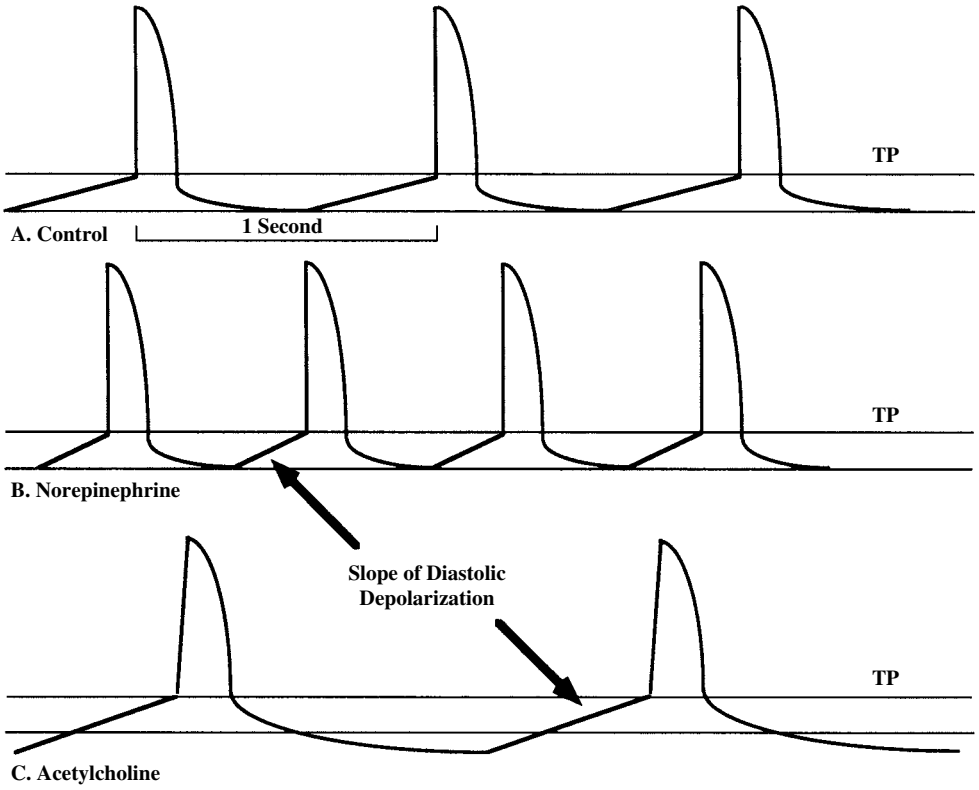

FIGURE 16.3

Effects of norepinephrine and acetylcholine on *spontaneous diastolic depolarization* (*automaticity*) in a pacemaker cell for the sinoatrial node. The pacemaker cell discharges spontaneously when the threshold potential (TP) is attained. The rate of spontaneous discharge is determined by the initial slope of the membrane potential and the time required to reach the threshold potential. A. Control recording showing the spontaneous diastolic depolarization. B. The effect of norepinephrine is to increase the slope of diastolic depolarization. The frequency of spontaneous discharge is increased. This effect is mediated through the activation of β-adrenoceptors in sinoatrial nodal cells. C. Acetylcholine stimulates muscarinic receptors in sinoatrial nodal cells. There is a decrease in the slope of diastolic depolarization as well as hyperpolarization of the cell. The time to reach the threshold potential is prolonged, with the net effect being a decrease in the rate of spontaneous depolarization.

tential, or hyperpolarization, of the sinoatrial cells. Thus, during vagal stimulation, the threshold potential of the sinoatrial node pacemaker cells is achieved more slowly and the heart rate is slowed.

Cardiac Conduction

The cardiac impulse begins in the sinoatrial node in the high lateral right atrium near the junction of the superior vena cava and the right atrium. Excitation leaves the sinoatrial node and spreads throughout the atrium. The myocytes (both atrial and ventricular) are long thin structures linked electrically via low-resistance pores known as gap junctions. The gap junctions are heterogeneously dispersed throughout the sarcolemmal membrane, although they are mainly concentrated on the ends of the myocytes. This distribution leads to polarity of the myocyte, with end-to-end conduction occurring at a more rapid rate than side-to-side (*anisotropic*) conduction. The difference in conduction velocity is up to a factor of three and may be important in supporting certain types of arrhythmias.

After the excitatory wave has spread throughout the atrium, it enters the atrioventricular (A-V) node. Importantly, the atrium and ventricle are electrically isolated from one another by a fibrous ring encircling the atrioventricular groove with the only connection occurring through the A-V node. If additional connections exist between the atrium and ventricle (accessory pathway), the potential for arrhythmia is present (atrioventricular reciprocating tachycardia), such as occurs with the Wolff-Parkinson-White syndrome. Conduction velocity slows significantly as the electrical signal enters the AV-node, where cellular depolarization depends on $I_{Ca}{}^{++}$ rather than I_{Na}. The delay in ventricular excitation allows the atria to contract and enhances the filling of the ventricle. After passing through the A-V node, the electrical signal is carried via the right and left bundle branches to the body of the right and left ventricles.

The principal determinant of conduction velocity within the myocardium is the maximum rate of depolarization (V_{max}) of phase 0 of the action potential in individual myocytes. The number of sodium channels that are recruited to open by a depolarizing stimulus determines the V_{max} in atrial and ventricular muscle. Changes in the configuration of the sodium channel in the sarcolemmal membrane at resting membrane potentials, which are more positive (depolarized) than −75mV, cause the channels to enter an inactivated state in which they cannot participate in an action potential. As a result, there is a reduction in the peak sodium current leading to a reduction in upstroke velocity, action potential amplitude, excitability, and conduction velocity. This has important ramifications for the genesis of arrhythmias. *One common clinical cause of depolarization of myocardial tissue is ischemia resulting from coronary artery disease.*

Refractory Period

Depolarized cardiac cells are transiently unresponsive to any activation stimuli. During this interval, most Na^+ and some Ca^{++} channels are inactivated, and the cardiac myocytes are said to be refractory. The refractory period is subdivided into three phases, absolute, effective, and relative. *The absolute refractory period* is the time from the onset of the action potential until a stimulus is able to evoke a local nonconducted response. During this period, the cell is completely refractory to any stimulus regardless of its intensity. The *effective refractory period* (*ERP*) begins with the onset of the action potential, incorporates the absolute refractory period, and ends when an excitatory stimulus is able to generate a conducted signal. The ERP is determined as the shortest interval between two stimuli of equal intensity that results in the generation of a propagated response. The *relative refractory period* begins with the completion of the ERP and continues through the time in which a signal may be conducted slowly, prior to obtaining normal propagation of the signal. Since the cell is not fully repolarized during the relative refractory period, a stronger than normal stimulus is needed to produce depolarization and conduction of a propagated impulse.

Pharmacological agents that impair the function of channels normally active during phase III repolarization exert their effects by prolonging the refractory period of the tissue, thereby prolonging the interval before the myocardial cells are capable of responding to a subsequent stimulus that will propagate in a normal manner. As the myocytes repolarize, they enter a relative refractory period during which they again can undergo depolarization. Normal conduction velocity resumes when cells are stimulated, having fully recovered at the end of the relative refractory period. *Thus, the membrane potential at which excitation of the cell occurs determines conduction velocity. Conducted impulses generated during the relative refractory period will propagate slowly and may contribute to the genesis of cardiac arrhythmias.*

Mechanisms of Arrhythmias

Disturbances in the orderly formation and conduction of the cardiac impulse may result in heart rates that are either too fast (tachycardia) or too slow (bradycardia). In general, bradyarrhythmias result from the failure of impulse generation within the sinoatrial node or failure of the excitatory wavefront to conduct from the atrium to the ventricle through the atrioventricular node. *In general, bradyarrhythmias are not amenable to long-term pharmacological therapy and may require permanent cardiac pacing.* Tachyarrhythmias, conversely, frequently may be palliated with long-term medical

therapy. The mechanisms supporting tachycardias may be classified broadly into three groups: (1) abnormal automaticity, (2) triggered activity, or (3) reentry.

Enhanced Automaticity

Automaticity, as outlined earlier, describes a cell's ability to raise spontaneously (depolarize) the resting membrane potential above the threshold value to initiate an action potential. Enhanced automaticity resulting in tachycardia may result from an increase in the slope of phase 4 depolarization or a decrease (less negative) in the resting membrane potential. Activation of β-adrenoceptors, hypokalemia, and stretching of cardiac cells all increase the slope of phase 4 depolarization and may serve as the trigger for enhanced automaticity. It is also possible for tissue that normally does not have pacemaking capabilities to develop inappropriate spontaneous diastolic depolarization and serve as an ectopic focus for impulse generation.

Triggered Activity

Triggered activity occurs when after-depolarizations induced by a preceding action potential raise the resting membrane potential above the threshold value, leading to an additional action potential. After-depolarizations may be categorized as early, occurring during phase III of the action potential before achieving full repolarization, or delayed, occurring after full repolarization of the membrane. After-depolarizations may stimulate an isolated extrapropagated impulse or lead to sustained repetitive activity. The crucial difference between triggered activity and abnormal automaticity is that triggered activity depends on a preceding action potential and cannot be self-induced. After-depolarizations or triggered activity are often associated with excessive increases in intracellular [Ca^{++}]. The potential for development of triggered activity is accentuated in the presence of an increase in extracellular [Ca^{++}] that would increase the amount of ionized calcium entering the cell during depolarization. Furthermore, conditions or pharmacological interventions favoring prolongation of the plateau (phase 3) of the action potential and prolongation of the QT interval of the electrocardiogram would increase intracellular [Ca^{++}] and the potential for proarrhythmia.

Early after-depolarizations are purported to be the mechanism giving rise to *torsades de pointes*. Conditions or drugs known to prolong the action potential, especially by interventions that decrease the outward potassium currents, facilitate development of torsades de pointes tachyarrhythmias. Early after-depolarizations may develop in association with hypokalemia, hypoxia, acidosis, and a wide range of pharmacological agents that interfere with outward currents or enhance inward currents. Antiarrhythmic agents, in particular sotalol, quinidine, and dofetilide, may give rise to after-depolarizations and torsades de pointes tachyarrhythmia in persons with underlying cardiac abnormalities or alterations in plasma electrolytes. Conditions leading to bradycardia also may facilitate development of torsades de pointes tachyarrhythmia.

Early after-depolarizations and the associated ventricular arrhythmia can be prevented or suppressed by the appropriate adjustment of plasma potassium and/or magnesium concentrations. Lidocaine or procainamide may be effective for termination of the arrhythmia.

Delayed after-depolarizations (Figure 16.4) may occur in the presence of a rapid heart rate, digitalis glycosides, hypokalemia, hypercalcemia and catecholamines. Each of these influences ultimately leads to an increase in intracellular ionized calcium that is known to activate an inward ionic current. The inward ionic current activates a nonselective channel that normally is involved with the transport of sodium but that under pathophysiological conditions may permit the movement of sodium or potassium ions. Upon reaching threshold, the calcium-induced oscillatory potentials lead to the production of a sustained ventricular arrhythmia. Delayed after-depolarizations, in contrast to early after-depolarizations, are more likely to produce triggered tachyarrhythmias during periods of short pacing cycle lengths (rapid heart rates). Exercise-induced ventricular tachycardia in persons without overt cardiac disease exemplifies such a situation. The electrophysiological abnormality is catecholamine dependent and calcium sensitive. The arrhythmia may respond to L-type calcium channel antagonists or inhibitors of the cardiac β-adrenoceptor. Each of these approaches would serve to reduce the tissue calcium concentration.

Reentry

Reentry is an abnormality of impulse conduction wherein an excitatory wavefront circulates around an inexcitable region. Figures 16.5 and 16.6 show a normally propagated and a reentrant event in injured ventricular myocardium, respectively. As illustrated in Figure 16.5, the wave of excitation passes through homogeneous tissue involving the Purkinje system (P_1 and P_2) and enters normal ventricular myocardium. As indicated in the figure, the wave of excitation conducts around an inexcitable barrier, collides within the tissue, and extinguishes within the ventricular myocardium. *A normally propagating impulse will enter ventricular myocardium nearly simultaneously at multiple regions where Purkinje fibers terminate in the walls of both ventricles.* The sequence of activation of the ventricular myocardium is rapid (~0.04 second). The net result is orderly activation of all ventricular myocardial fibers, giving rise to normal-appearing action potentials in the respective regions and a normal electrocardiogram.

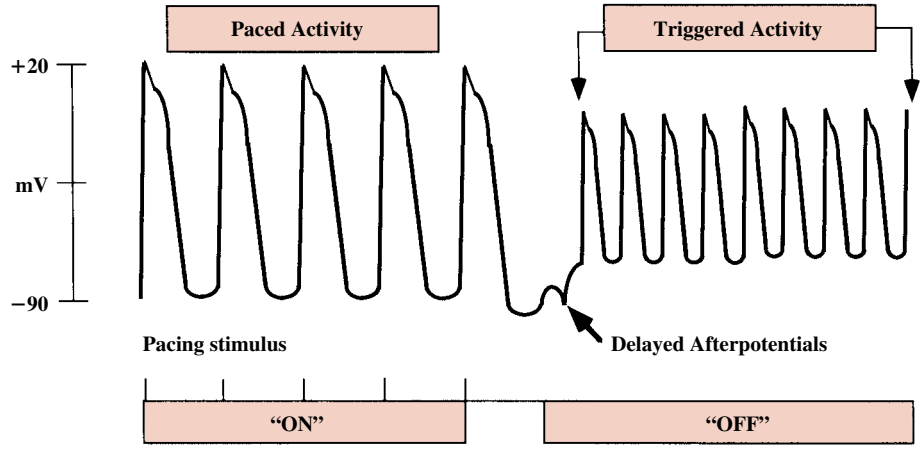

FIGURE 16.4
An example of *triggered activity* developing in Purkinje tissue. The appearance of a *delayed afterdepolarization* (*DAD*) after the fifth paced impulse is followed by a burst of triggered activity that maintains the rapid rate of impulse formation despite the cessation of electrical pacing. Triggered activity from DADs occurs in Purkinje fibers or ventricular muscle when the tissues are exposed to toxic concentrations of digitalis, catecholamines, or other interventions that increase intracellular calcium concentrations. Whereas DADs occur after the cell has achieved its maximum diastolic potential, the phenomenon of *early afterdepolarization* (*EADs*) occurs before complete repolarization has taken place. EADs can occur after exposure to drugs that prolong the action-potential duration and may account for the *proarrhythmic action* (discussed in the text) of several antiarrhythmic drugs.

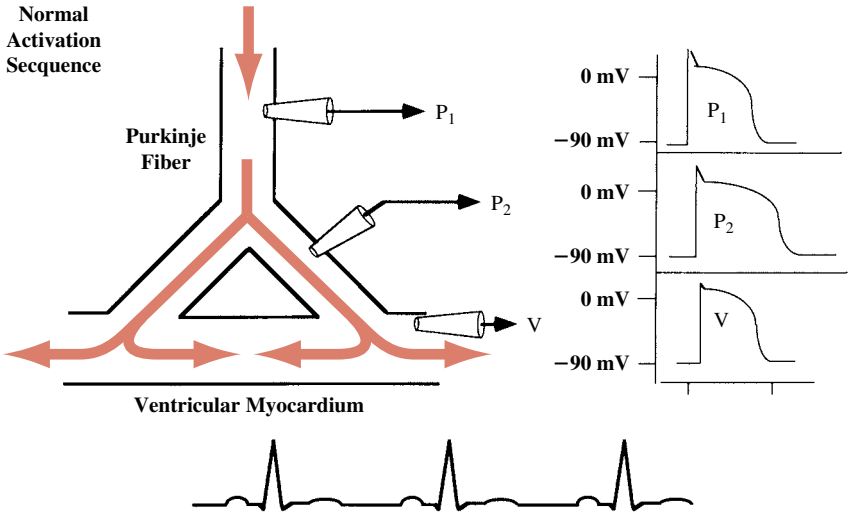

FIGURE 16.5
Schematic representation of normal activation and impulse transmission through the His-Purkinje system with final entry into ventricular myocardium. Intracellular recording electrodes are placed in the proximal Purkinje network (P_1), in the Purkinje branch on the right of the diagram (P_2), and in ventricular myocardium (V). The inset to the right illustrates the membrane action-potential recordings from the respective microelectrodes. The action-potential duration, and thus the effective refractory period, is longest in the more distal portion of the Purkinje branch immediately before insertion into the ventricular myocardium. Under normal conditions, the impulses within the terminal Purkinje network conduct with relatively equal velocities so as to activate the ventricular myocardium in a uniform manner. The longer duration of the effective refractory period in the terminal Purkinje fiber prevents the impulse, traversing within ventricular myocardium, from reentering the Purkinje network in the retrograde direction. The many wave fronts of excitation invading the ventricular myocardium from multiple insertions of the Purkinje network will collide in the ventricular myocardium and terminate. The net result is a homogeneous and nearly simultaneous activation of the entire ventricular myocardium within 400 msec. The electrocardiographic tracing below illustrates a normal sinus rhythm in which there is a repetitive and coordinated activation of the entire heart. One conducted sinoatrial impulse entering the ventricle from the atrioventricular node distributes over the His-Purkinje system to elicit one QRS complex indicating depolarization of the ventricular myocardium.

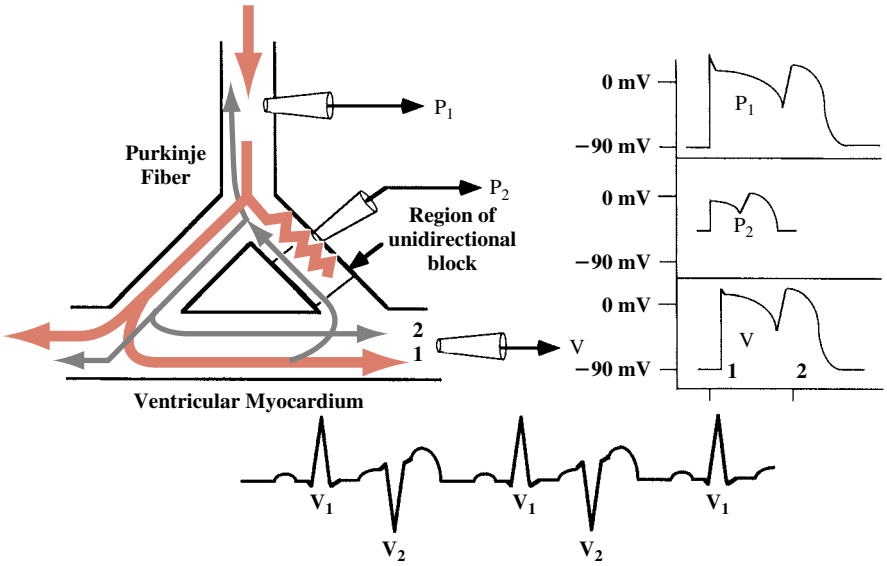

FIGURE 16.6
Conduction disorders due to *reentry* as might occur in the ischemic or postinfarcted myocardium. See Fig. 16.5 for a description of the format. As in the previous figure, *antegrade conduction* occurs in a normal manner over the proximal Purkinje system (P_1) and in the distal Purkinje network on the left of the diagram. However, the Purkinje network on the right (P_2) has been subjected to injury. The intracellular recordings from the respective electrodes indicate that the resting membrane potential from P_2 is decreased due to the presence of injury at this site. Therefore, the impulse conducts slowly and decrementally, and finally is blocked in the area of injury (*unidirectional block*). The ventricular myocardium, however, has been depolarized from normally conducting Purkinje fibers at remote insertion sites. The excitatory impulses traversing within the ventricular myocardium will reenter the distal portion of the Purkinje network (right side of diagram) and conduct slowly in the retrograde direction through the area of unidirectional block. The appropriate conditions are established by the conduction velocities and refractory periods in the respective tissues. The retrograde impulse can reenter the proximal Purkinje system and initiate reexcitation of the proximal and distal Purkinje network as well as the ventricular myocardium if each of these sites has recovered its excitability from the previous depolarization. The reentry impulse may give rise to a *premature coupled ventricular complex* in which the normally conducted impulse (V_1) is followed with precise timing by a *reentry ventricular complex* (V_2). The reentry impulses could occur more frequently so that the cardiac rhythm becomes dominated by the activity in the reentry pathway, thus leading to a rapid, repetitive series of ventricular complexes (*ventricular tachycardia*) in which the ventricular rate becomes rapid (>100 beats min) and may degenerate into ventricular fibrillation. The object of antiarrhythmic drug therapy is to reduce the frequency of hemodynamically disturbing premature ventricular impulses and to prevent the establishment of a sustained and rapidly conducting reentrant rhythm capable of becoming lethal.

In the undamaged myocardium, cardiac impulses travel rapidly antegrade through the Purkinje fibers to deliver the excitatory electrical impulse to the ventricular myocardium. During the normal activation sequence, retrograde conduction from ventricular myocardium to the conducting fibers is prevented by the longer duration of the membrane action potential and thus the refractory period in the Purkinje fibers.

In the presence of myocardial ischemia, propagation of cardiac impulses may be interfered with and a functional unidirectional block may occur. Impulses may fail to conduct longer in the anterograde direction to excite the more distal ventricular myocardium. Thus, the terminal segments of the Purkinje fibers within the affected region may be activated by impulses passing from the ventricular myocardium to conduct in a retrograde direction (impulse 1, Fig. 16.6), albeit at a slower rate of conduction. In some situations, the retrograde impulse will enter an area of normal myocardium sufficiently repolarized that it is no longer refractory, and a propagated action potential will result. The generation of an action potential may produce an increased rate of ventricular activation and may become self-sustaining. The latter phenomenon is known as a *reentrant,* or *circus, rhythm.* If propagation is too rapid through the region of myocardial damage, the retrograde impulse will

attempt to reenter the normal region while the tissue is refractory. This will give rise to bidirectional block, terminating the reentrant wave front. Therefore, for *reentry* to occur, there must be a region of *unidirectional block* and *slow conduction.* The delay in conduction permits the tissue ahead of the advancing wave front to regain its excitability, sustaining the reentry circuit. As shown in Figure 16.6, the reentrant wave front gives rise to a second depolarizing impulse (2) in the ventricular myocardium and in each of the branches of the Purkinje network (P_1 and P_2). The net result of the reentrant wave is depicted in the electrocardiogram (ECG), in which coupled ventricular premature complexes (V_2) follow each normal (V_1) complex.

It is estimated that 80 to 90% of clinical arrhythmias have a reentry mechanism. One explanation of how an antiarrhythmic agent may abolish reentry is by converting unidirectional block to bidirectional block. A second mechanism to explain the action of antiarrhythmic drugs is that they can prevent reentry by increasing the ERP of the cardiac fibers within or surrounding the region of the reentrant circuit.

CLASSIFICATION OF ANTIARRHYTHMIC DRUGS

Antiarrhythmic drugs have historically been segregated by the Vaughn Williams classification system into four main groups, based on their predominant mechanism of action. This is a good starting point for organizing one's thinking about the various antiarrhythmic drugs, but it is a great oversimplification and does not address several drugs that have electrophysiological effects characteristic of more than one group. Thus, although the grouping of antiarrhythmic agents into four classes is convenient, such a classification falls short of explaining the underlying mechanisms by which many drugs ultimately exert their therapeutic antiarrhythmic effect. Also, certain agents do not fall neatly into the four classes; these are discussed at the end of the chapter.

Class I Drugs

Class I antiarrhythmic drugs are characterized by their ability to block the voltage-gated sodium channel. The class I agents may block the channel when it is in either the open or the inactivated state. Inhibition of the sodium channel results in a decrease in the rate of rise of phase 0 of the cardiac membrane action potential and a slowing of the conduction velocity. Additionally, class I drugs, through inhibition of the sodium channel, require that a more hyperpolarized membrane potential (more negative) be achieved before the membrane becomes excitable and can propagate an excitatory stimulus. As a result, the ERP of fast-response fibers is prolonged. Although many class I antiarrhythmic drugs possess local anesthetic actions and can depress myocardial contractile force, these effects are usually observed only at higher plasma concentrations.

The antiarrhythmic drugs in class I suppress both normal Purkinje fiber and His bundle automaticity in addition to abnormal automaticity resulting from myocardial damage. Suppression of abnormal automaticity permits the sinoatrial node again to assume the role of the dominant pacemaker.

The antiarrhythmic agents that belong to class I are divided into three subgroups (Table 16.1) with slightly different properties. Class IA drugs slow the rate of rise of phase 0 ($V_{max>}$) of the action potential and prolong the ventricular ERP. Members of this class impair the function of the membrane sodium channel, thereby decreasing the number of channels available for membrane depolarization. Class IA drugs do not alter the resting membrane potential. Because they decrease $V_{max>}$, class IA drugs slow conduction velocity. Members of this class directly decrease the slope of phase 4 depolarization in pacemaker cells, especially those that arise outside of the sinoatrial node.

Members of class IB have a minimal effect on the rate of depolarization and are characterized by their ability to decrease the duration of action potential and ERP of Purkinje fibers. Members of this class have a minimal effect on conduction velocity in ventricular myocardium and are without apparent effect on refractoriness.

The drugs in class IC produce a marked depression in the rate of rise of the membrane action potential and have minimal effects on the duration of membrane action potential and ERP of ventricular myocardial cells.

Class II Drugs

Class II antiarrhythmic drugs competitively inhibit β-adrenoceptors and inhibit catecholamine-induced stimulation of cardiac β-receptors. In addition, some members of the group (e.g., propranolol and acebutolol) cause electrophysiological alterations in Purkinje fibers that resemble those produced by class I antiarrhythmic drugs. The latter actions have been called membrane-stabilizing effects.

Class III Drugs

Class III antiarrhythmic drugs prolong the membrane action potential by delaying repolarization without altering phase 0 of depolarization or the resting membrane potential. Class III drugs have a significant risk of proarrhythmia because of the prolongation of action potential and the induction of torsades de pointes.

TABLE 16.1 Classification of Antiarrhythmic Drugs

Antiarrhythmic Class	Representative Drug	Principal Pharmacological Effects
IA	Quinidine Procainamide Disopyramide Moricizine[a]	Decrease V_{max} of phase 0, increase refractory period, moderately decrease conduction velocity, decrease fast inward sodium current, inhibit potassium repolarization current.
IB	Lidocaine Phenytoin Tocainide Moricizine[a] Mexiletine	Minimally change V_{max} of phase 0, decrease cardiac action potential duration, decrease inward sodium current in ventricular muscle, increase outward potassium current.
IC	Flecainide Propafenone	Markedly decrease V_{max} of phase 0, profoundly decrease ventricular conduction velocity, markedly inhibit inward sodium current. High potential for proarrhythmia.
II	Propranolol Metoprolol Nadolol Acebutolol Atenolol Pindolol Timolol Sotalol Esmolol[b]	β-Adrenoceptor antagonist, cardiac membrane stabilization, indirect effect on sinoatrial node to decrease rate of spontaneous diastolic depolarization. Indirect effect on A-V node to decrease conduction velocity and prolong ERP.
III	Amiodarone Bretylium Sotalol	Prolong ventricular action potential, prolong refractoriness, inhibit potassium repolarization currents. Prolong QTc interval. Potential for proarrhythmia (torsades de pointes tachyarrhythmia).
IV	Ibutilide Dofetilide Verapamil Diltiazem Bepridil[c]	Inhibit the slow inward calcium current, minimal effect (decrease) on ventricular action potential, major effects on the atrioventricular node to slow conduction velocity and increase the ERP.

[a]Mixed class IA/IB drug.
[b]Ultra–short-acting β-adrenoceptor blocking agent.
[c]May also show class III activity.

Class IV Drugs

Class IV drugs block the slow inward Ca^{++} current (L-type calcium channel) in cardiac tissue. The most pronounced electrophysiological effects are exerted on cardiac cells that depend on the Ca^{++} channel for initiating the action potential, such as those found in the sinoatrial and A-V nodes. The administration of class IV drugs slows conduction velocity and increases refractoriness in the A-V node, thereby reducing the ability of the A-V node to conduct rapid impulses to the ventricle. This action may terminate supraventricular tachycardias and can slow conduction during atrial flutter or fibrillation.

CLASS IA

Quinidine

Quinidine is an alkaloid obtained from various species of *Cinchona* or its hybrids, from *Remijia pedunculata,* or from quinine. Quinidine is the dextrorotatory isomer of quinine.

Quinidine (*Quinidex*) was one of the first clinically used antiarrhythmic agents. Because of the high incidence of ventricular proarrhythmia associated with its use and numerous other equally efficacious agents, quinidine is now used sparingly. Quinidine shares all of the pharmacological properties of quinine, including antimalarial, antipyretic, oxytocic, and skeletal muscle relaxant actions.

Electrophysiological Actions

Quinidine's effect on the electrical properties of a particular cardiac tissue depends on the extent of parasympathetic innervation, the level of parasympathetic tone, and the dose. The anticholinergic actions of quinidine predominate at lower plasma concentrations. Later, when steady-state therapeutic plasma concentrations have been achieved, the drug's direct electrophysiological actions predominate. The direct and indirect electrophysiological actions are summarized in Table 16.2.

TABLE 16.2 Cardiac Electrophysiological Effects of Class I Antiarrhythmic Drugs

Drug	Class	Atria	S-A Node	A-V Node	His-Purkinje	Ventric Muscle	APD	ERP
Quinidine	IA	D	—	D	D	D	Increased	Increased
Procainamide	IA	D	—	D	D	D		Increased
Disopyramide	IA	D	—	D/I[a]	—	D	Increased	Increased/ decreased[a]
Moricizine	IA	—	—	D	D			
Lidocaine	IB	D	—	D	D	D	Decreased (His-Purkinje)	No effect Decreased
Phenytoin	IB	—/D	—	I			Decreased	Decreased
Tocainide	IB				D			
Mexiletine	IB				D		Decreased	Decreased
Encainide	IC		D	D	D	D		
Flecainide	IC	D	—	I	D	D		
Propafenone	IC	D	D	D	D	D		Increased

[a]Dependent upon degree of anticholinergic action.
K, decrease in conduction velocity; I, increase in conduction velocity; —, no known conduction effects; APD, action potential duration; ERP, effective refractory period (ventricular).

Sinoatrial Node and Atrial Tissue

The indirect effect of quinidine on the sinoatrial node is a result of the drug's potential to exert an anticholinergic action resulting in a slight increase in heart rate. Higher concentrations of quinidine have a direct effect of depressing the rate of spontaneous diastolic depolarization.

Quinidine administration results in a dose-dependent depression of membrane responsiveness in atrial muscle fibers. The maximum rate of phase 0 depolarization and the amplitude of phase 0 are depressed equally at all membrane potentials. Quinidine also decreases atrial muscle excitability in such a way that a larger current stimulus is needed for initiation of an active response. These actions of quinidine often are referred to as its local anesthetic properties.

A-V Node

Both the direct and indirect actions of quinidine are important in determining its ultimate effect on A-V conduction. The indirect (anticholinergic) properties of quinidine prevent both vagally mediated prolongation of the A-V node refractory period and depression of conduction velocity; these effects lead to enhancement of A-V transmission. Quinidine's direct electrophysiological actions on the A-V node are to decrease conduction velocity and increase the ERP.

His-Purkinje System and Ventricular Muscle

Quinidine can depress the automaticity of ventricular pacemakers by depressing the slope of phase 4 depolarization. Depression of pacemakers in the His-Purkinje system is more pronounced than depression of sinoatrial node pacemaker cells.

Quinidine also prolongs repolarization in Purkinje fibers and ventricular muscle, increasing the duration of the action potential. As in atrial muscle, quinidine administration results in postrepolarization refractoriness, that is, an extension of refractoriness beyond the recovery of the resting membrane potential. The indirect (anticholinergic) properties of quinidine are not a factor in its actions on ventricular muscle and the His-Purkinje system.

Serum K^+ concentrations have a major influence on the activity of quinidine on cardiac tissue. Low extracellular K^+ concentrations antagonize the depressant effects of quinidine on membrane responsiveness, whereas high extracellular K^+ concentrations increase quinidine's ability to depress membrane responsiveness. This dependency may explain why hypokalemic patients are often unresponsive to the antiarrhythmic effects of quinidine and are prone to develop cardiac rhythm disorders.

Electrocardiographic Changes

At normal therapeutic plasma concentrations, quinidine prolongs the PR, the QRS, and the QT intervals. QRS and QT prolongations are more pronounced with quinidine than with most other antiarrhythmic agents. The magnitude of these changes is related directly to the plasma quinidine concentration.

Hemodynamic Effects

Although myocardial depression is not a problem in patients with normal cardiac function, in patients with compromised myocardial function, quinidine may depress cardiac contractility sufficiently to result in a de-

crease in cardiac output, a significant rise in left ventricular end-diastolic pressure, and overt heart failure. Quinidine can relax vascular smooth muscle directly as well as indirectly by inhibition of α_1-adrenoceptors. The depressant effects of quinidine on the cardiovascular system are most likely to occur after IV administration, and therefore, quinidine should not be employed routinely in the emergency treatment of arrhythmias. Because of its potential to cause marked depression of myocardial contractility and to decrease peripheral vascular resistance, parenteral administration of quinidine is seldom indicated.

Pharmacokinetics

The pharmacokinetic characteristics of quinidine:

Oral bioavailability	Almost complete absorption
Onset of action	1–3 hours
Peak response	1–2 hours
Duration of action	6–8 hours
Plasma half-life	6 hours
Primary route of metabolism	Hepatic; active metabolite
Primary route of excretion	10–50% renal (unchanged)
Therapeutic serum concentration	2–4 μg /mL

Clinical Uses

Primary indications for the use of quinidine include (1) abolition of premature complexes that have an atrial, A-V junctional, or ventricular origin; (2) restoration of normal sinus rhythm in atrial flutter and atrial fibrillation after controlling the ventricular rate with digitalis; (3) maintenance of normal sinus rhythm after electrical conversion of atrial arrhythmias; (4) prophylaxis against arrhythmias associated with electrical countershock; (5) termination of ventricular tachycardia; and (6) suppression of repetitive tachycardia associated with Wolff-Parkinson-White (WPW) syndrome.

Although quinidine often is successful in producing normal sinus rhythm, its administration in the presence of a rapid atrial rate (flutter and possibly atrial fibrillation) can lead to a further and dangerous increase in the ventricular rate secondary to inhibition of basal vagal tone upon the A-V node. For this reason, *digitalis should be used before quinidine when one is attempting to convert atrial flutter or atrial fibrillation to normal sinus rhythm.*

Adverse Effects

The most common adverse effects associated with quinidine administration are diarrhea (35%), upper gastrointestinal distress (25%), and light-headedness (15%). Other relatively common adverse effects include fatigue, palpitations, headache (each occurring with an incidence of 7%), anginalike pain, and rash. These adverse effects are generally dose related and reversible with cessation of therapy. In some patients, quinidine administration may bring on thrombocytopenia due to the formation of a plasma protein–quinidine complex that evokes a circulating antibody directed against the blood platelet. Although platelet counts return to normal on cessation of therapy, administration of quinidine or quinine at a later date can cause the reappearance of thrombocytopenia.

The cardiac toxicity of quinidine includes A-V and intraventricular block, ventricular tachyarrhythmias, and depression of myocardial contractility. Ventricular arrhythmia induced by quinidine leading to a loss of consciousness has been referred to as quinidine syncope. This devastating side effect is more common in women than in men and may occur at therapeutic or subtherapeutic plasma concentrations.

Large doses of quinidine can produce a syndrome known as *cinchonism,* which is characterized by ringing in the ears, headache, nausea, visual disturbances or blurred vision, disturbed auditory acuity, and vertigo. Larger doses can produce confusion, delirium, hallucinations, or psychoses. Quinidine can decrease blood glucose concentrations, possibly by inducing insulin secretion.

Contraindications

One of the few absolute contraindications for quinidine is complete A-V block with an A-V pacemaker or idioventricular pacemaker; this may be suppressed by quinidine, leading to cardiac arrest.

Persons with congenital QT prolongation may develop torsades de pointes tachyarrhythmia and should not be exposed to quinidine.

Owing to the negative inotropic action of quinidine, it is contraindicated in congestive heart failure and hypotension.

Digitalis intoxication and hyperkalemia can accentuate the depression of conduction caused by quinidine.

Myasthenia gravis can be aggravated severely by quinidine's actions at the neuromuscular junction.

The use of quinidine and quinine should be avoided in patients who previously showed evidence of quinidine-induced thrombocytopenia.

Drug Interactions

Quinidine can increase the plasma concentrations of digoxin, which may in turn lead to signs and symptoms of digitalis toxicity. Gastrointestinal, central nervous system (CNS), or cardiac toxicity associated with elevated digoxin concentrations may occur. Quinidine and digoxin can be administered concurrently; however, a downward adjustment in the digoxin dose may be required.

Drugs that have been associated with elevations in quinidine concentrations include acetazolamide, the antacids magnesium hydroxide and calcium carbonate, and the H_2-receptor antagonist cimetidine. Cimetidine inhibits the hepatic metabolism of quinidine. Phenytoin, rifampin, and barbiturates increase the hepatic metabolism of quinidine and reduce its plasma concentrations.

Procainamide

Procainamide (*Pronestyl, Procan SR*) is a derivative of the local anesthetic agent procaine. Procainamide has a longer half-life, does not cause CNS toxicity at therapeutic plasma concentrations, and is effective orally. *Procainamide is a particularly useful antiarrhythmic drug, effective in the treatment of supraventricular, ventricular, and digitalis-induced arrhythmias.*

Electrophysiological Actions

Table 16.2 describes the direct, indirect, and net actions of procainamide on cardiac electrophysiology.

Hemodynamic Effects

The hemodynamic alterations produced by procainamide are similar to those of quinidine but are not as intense. Alterations in circulatory dynamics vary according to the cardiovascular state of the individual. The hypotensive effects of procainamide are less pronounced after intramuscular administration and seldom occur after oral administration.

Pharmacokinetics

The pharmacokinetic characteristics of procainamide:

Oral bioavailability	75–95%
Onset of action	5–10 minutes
Peak response	60–90 minutes
Duration of action	4–10 hours
Plasma half-life	2.5–4.5 hours
Primary route of metabolism	Hepatic; active metabolite
Primary route of excretion	50–60% renal (unchanged)
Therapeutic serum concentration	4–10 μg /mL

Clinical Uses

Procainamide is an effective antiarrhythmic agent when given in sufficient doses at relatively short (3–4 hours) dosage intervals. *Procainamide is useful in the treatment of premature atrial contractions, paroxysmal atrial tachycardia, and atrial fibrillation of recent onset.* Procainamide is only moderately effective in converting atrial flutter or chronic atrial fibrillation to sinus rhythm, although it has value in preventing recurrences of these arrhythmias once they have been terminated by direct current (DC) cardioversion.

Procainamide can decrease the occurrence of all types of active ventricular dysrhythmias in patients with acute myocardial infarction who are free from A-V dissociation, serious ventricular failure, and cardiogenic shock. About 90% of patients with ventricular premature contractions and 80% of patients with ventricular tachycardia respond to procainamide administration.

Although the spectrum of action and electrophysiological effects of quinidine and procainamide are similar, the relatively short duration of action of procainamide has tended to restrict its use to patients who are intolerant of or unresponsive to quinidine.

Adverse Effects

Acute cardiovascular reactions to procainamide administration include hypotension, A-V block, intraventricular block, ventricular tachyarrhythmias, and complete heart block. The drug dosage must be reduced or even stopped if severe depression of conduction (severe prolongation of the QRS interval) or repolarization (severe prolongation of the QT interval) occurs.

Long-term drug use leads to increased antinuclear antibody titers in more than 80% of patients; more than 30% of patients receiving long-term procainamide therapy develop a clinical lupus erythematosus–like syndrome. The symptoms may disappear within a few days of cessation of procainamide therapy, although the tests for antinuclear factor and lupus erythematosus cells may remain positive for several months.

Procainamide, unlike procaine, has little potential to produce CNS toxicity. Rarely, patients may be confused or have hallucinations.

Contraindications

Contraindications to procainamide are similar to those for quinidine. Because of its effects on A-V nodal and His-Purkinje conduction, procainamide should be administered with caution to patients with second-degree A-V block and bundle branch block. Procainamide should not be administered to patients who have shown procaine or procainamide hypersensitivity and should be used with caution in patients with bronchial asthma. Prolonged administration should be accompanied by hematological studies, since agranulocytosis may occur.

Drug Interactions

The inherent anticholinergic properties of procainamide may interfere with the therapeutic effect of cholinergic agents. Patients receiving cimetidine and procainamide may exhibit signs of procainamide toxicity, as cimetidine inhibits the metabolism of procainamide. Simultaneous

use of alcohol will increase the hepatic clearance of procainamide. Procainamide may enhance or prolong the neuromuscular blocking activity of the aminoglycosides with the potential of producing respiratory depression. The simultaneous administration of quinidine or amiodarone may increase the plasma concentration of procainamide.

Disopyramide

Disopyramide (*Norpace*) can suppress atrial and ventricular arrhythmias and is longer acting than other drugs in its class.

Electrophysiological Actions

The effects of disopyramide on the myocardium and specialized conduction tissue (Table 16.2) are a composite of its direct actions on cardiac tissue and its indirect actions mediated by competitive blockade of muscarinic cholinergic receptors.

Sinoatrial Node

The direct depressant actions of disopyramide on the sinoatrial node are antagonized by its anticholinergic properties, so that at therapeutic plasma concentrations, either no change or a slight increase in sinus heart rate is observed. Both the anticholinergic and direct depressant actions of disopyramide on sinus automaticity appear to be greater than those of quinidine.

Atrium

Disopyramide reduces membrane responsiveness in atrial muscle and the amplitude of the action potential. Excitability of atrial muscle is decreased. These changes decrease atrial muscle conduction velocity. Action potential duration in atrial muscle fibers is prolonged by disopyramide administration. This occurrence increases ERP. Postrepolarization refractoriness does not occur with disopyramide, and it appears to differ from quinidine and procainamide in this respect.

Abnormal atrial automaticity may be abolished at disopyramide plasma concentrations that fail to alter either conduction velocity or refractoriness. Disopyramide increases atrial refractoriness in patients pretreated with atropine, suggesting that the primary action of disopyramide is a direct one and not a consequence of its anticholinergic effect.

A-V Node

Disopyramide depresses conduction velocity and increases the ERP of the A-V node through a direct action. Its anticholinergic actions, however, produce an increase in conduction velocity and a decrease in the ERP. The net effect of disopyramide on A-V nodal transmission therefore will be determined by the sum of its direct depression and indirect facilitation of transmission.

His-Purkinje System and Ventricular Muscle

Disopyramide administration reduces membrane responsiveness in Purkinje fibers and ventricular muscle and reduces the action potential amplitude. Even greater depression may occur in damaged or injured myocardial cells. Action potentials are prolonged after disopyramide administration, and this results in an increase in the ERPs of His-Purkinje and ventricular muscle tissue. Unlike procainamide and quinidine, disopyramide does not produce postrepolarization refractoriness.

The effect of disopyramide on conduction velocity depends on extracellular K^+ concentrations. Hypokalemic patients may respond poorly to the antiarrhythmic action of disopyramide, whereas hyperkalemia may accentuate the drug's depressant actions.

Electrocardiographic Changes

The electrocardiographic changes observed after disopyramide administration are identical to those seen with quinidine and procainamide.

Hemodynamic Effects

Disopyramide directly depresses myocardial contractility. The negative inotropic effect may be detrimental in patients with compromised cardiac function. Some patients develop overt congestive heart failure. At usual therapeutic doses, depression of myocardial function is not a problem in most patients with normal ventricular function.

Despite the decrease in cardiac output produced by disopyramide, blood pressure is well maintained by a reflex increase in vascular resistance. Catecholamine administration can reverse the myocardial depression.

Pharmacokinetics

The salient pharmacokinetic features of disopyramide:

Oral bioavailability	87–95%
Onset of action	30 minutes–3.5 hours
Peak response	30 minutes–3 hours
Duration of action	1.5–8.5 hours
Plasma half-life	4–10 hours
Primary route of metabolism	Hepatic, active metabolite
Primary route of excretion	80% renal (50% unchanged); 15% biliary
Therapeutic serum concentration	1–5 μg /mL

Clinical Uses

The indications for use of disopyramide are similar to those for quinidine, except that it is not approved for use in the prophylaxis of atrial flutter or atrial fibrillation after DC conversion. The indications are as follows: unifocal premature (ectopic) ventricular contractions, premature (ectopic) ventricular contractions of multifocal origin, paired premature ventricular contractions (couplets), and episodes of ventricular tachycardia. Persistent ventricular tachycardia is usually treated with DC conversion.

Adverse Effects

The major toxic reactions to disopyramide administration include hypotension, congestive heart failure, and conduction disturbances. These effects are the result of disopyramide's ability to depress myocardial contractility and myocardial conduction. Although disopyramide initially may produce ventricular tachyarrhythmias or ventricular fibrillation in some patients, the incidence of disopyramide-induced syncope in long-term therapy is not known. Most other toxic reactions (e.g., dry mouth, blurred vision, constipation) can be attributed to the anticholinergic properties of the drug.

CNS stimulation and hallucinations are rare. The incidence of severe adverse effects in long-term therapy may be lower than those observed with quinidine or procainamide.

Contraindications

Disopyramide should not be administered in cardiogenic shock, preexisting second- or third-degree A-V block, or known hypersensitivity to the drug. Neither should it be given to patients who are poorly compensated or those with uncompensated heart failure or severe hypotension. Because of its ability to slow cardiac conduction, disopyramide is not indicated for the treatment of digitalis-induced ventricular arrhythmias. Patients with congenital prolongation of the QT interval should not receive quinidine, procainamide, or disopyramide because further prolongation of the QT interval may increase the incidence of ventricular fibrillation.

Because of its anticholinergic properties, disopyramide should not be used in patients with glaucoma. Urinary retention and benign prostatic hypertrophy are also relative contraindications to disopyramide therapy. Patients with myasthenia gravis may have a myasthenic crisis after disopyramide administration as a result of the drug's local anesthetic action at the neuromuscular junction. The elderly patient may exhibit increased sensitivity to the anticholinergic actions of disopyramide.

Caution is advised when disopyramide is used in conjunction with other cardiac depressant drugs, such as verapamil, which may adversely affect atrioventricular conduction.

Drug Interactions

In the presence of phenytoin, the metabolism of disopyramide is increased (reducing its effective concentration) and the accumulation of its metabolites is also increased, thereby increasing the probability of anticholinergic adverse effects. Rifampin also stimulates the hepatic metabolism of disopyramide, reducing its plasma concentration.

Unlike quinidine, disopyramide does not increase the plasma concentration of digoxin in patients receiving a maintenance dose of the cardiac glycoside. Hypoglycemia has been reported with the use of disopyramide, particularly in conjunction with moderate or excessive alcohol intake.

Moricizine

Moricizine (*Ethmozine*) is an antiarrhythmic used to treat documented life-threatening arrhythmias.

Electrophysiological Actions

Moricizine exerts electrophysiological effects that are common to both class IA and IB agents. However, it does not belong in any of the existing drug classes.

Sinoatrial Node

No significant effect of moricizine is noted on the sinus cycle length or on automaticity within the sinoatrial node.

Atria

Moricizine does not affect the atrial refractory period or conduction velocity within atrial muscle.

A-V Node

Moricizine depresses conduction and prolongs refractoriness in the atrioventricular node and in the infranodal region. These changes are manifest in a prolongation of the PR interval on the electrocardiogram.

His-Purkinje System and Ventricular Muscle

The primary electrophysiological effects of moricizine relate to its inhibition of the fast inward sodium channel. Moricizine reduces the maximal upstroke of phase 0 and shortens the cardiac transmembrane action potential. The sodium channel blocking effect of moricizine is more significant at faster stimulation rates; an action referred to as use dependence. This phenomenon may explain the efficacy of moricizine in suppressing rapid ectopic activity. An interesting effect of moricizine is its depressant effect on automaticity in ischemic

Purkinje tissue in contrast to its inability to alter the slope of phase 4 depolarization of spontaneous automatic Purkinje fibers.

Electrocardiographic Changes

The electrocardiographic effects of moricizine include alterations in conduction velocity without an effect on the refractoriness of heart tissue. Moricizine enhances sinus node automaticity and prolongs sinoatrial and His-Purkinje intervals and the QRS. Moricizine prolongs ventricular conduction, thereby widening the QRS complex on the electrocardiogram. It has no significant effects on the QT interval.

The administration of moricizine is not associated with clinically significant hemodynamic effects.

Pharmacokinetics

The characteristics of moricizine:

Oral bioavailability	Not known
Onset of action	Within 2 hours
Peak response	6 hours
Duration of action	10–24 hours
Plasma half-life	1.5–3.5 hours
Primary route of metabolism	Hepatic
Primary route of excretion	56% biliary /fecal; 39% renal
Therapeutic serum concentration	Not established

Clinical Uses

Moricizine is indicated for the treatment of documented ventricular arrhythmias, particularly sustained ventricular tachycardia. Moricizine was evaluated in the CAST II clinical trial for the prevention of postinfarction ventricular premature complexes. It was ineffective and found to be proarrhythmic. Patients in the moricizine arm of the trial exhibited a greater incidence of sudden cardiac death than did controls.

Adverse Effects

The principal adverse gastrointestinal effect of moricizine is nausea (7%). Abdominal discomfort has also been reported. Dizziness (11%) is the most frequently reported CNS-related adverse effect. Such reactions increase in frequency with prolonged drug administration.

As with other antiarrhythmic drugs, moricizine has proarrhythmic activity, which may manifest as new ventricular ectopic beats or a worsening of preexisting ventricular arrhythmias. These effects are most common in patients with depressed left ventricular function and a history of congestive heart failure. Cardiovascular effects requiring drug withdrawal include conduction defects, sinus pauses, junctional rhythm, and A-V block.

Contraindications

Patients with preexisting second- or third-degree A-V block, cardiogenic shock, or drug hypersensitivity should not be treated with moricizine.

Drug Interactions

Clinically significant interactions with moricizine do not appear to exist.

CLASS IB

Lidocaine

Lidocaine (*Xylocaine*) was introduced as a local anesthetic and is still used extensively for that purpose (see Chapter 27). *Lidocaine is an effective sodium channel blocker, binding to channels in the inactivated state.* Lidocaine, like other IB agents, acts preferentially in diseased (ischemic) tissue, causing conduction block and interrupting reentrant tachycardias.

Electrophysiological Actions

Sinoatrial Node

When administered in normal therapeutic doses (1–5 mg/kg), lidocaine has no effect on the sinus rate.

Atrium

The electrophysiological properties of lidocaine in atrial muscle resemble those produced by quinidine. Membrane responsiveness, action potential amplitude, and atrial muscle excitability are all decreased. These changes result in a decrease in conduction velocity. However, the depression of conduction velocity is less marked than that caused by quinidine or procainamide. Action potential duration of atrial muscle fibers is not altered by lidocaine at either normal or subnormal extracellular K^+ levels. The ERP of atrial myocardium either remains the same or increases slightly after lidocaine administration.

A-V Node

Lidocaine minimally affects both the conduction velocity and the ERP of the A-V node. Lidocaine does not possess anticholinergic properties and will not improve A-V transmission when atrial flutter or atrial fibrillation is present.

His-Purkinje System and Ventricular Muscle

Lidocaine reduces action potential amplitude and membrane responsiveness. Significant shortening of the action potential duration and ERP occurs at lower con-

centrations of lidocaine in Purkinje fibers than in ventricular muscle. Lidocaine in very low concentrations slows phase 4 depolarization in Purkinje fibers and decreases their spontaneous rate of discharge. In higher concentrations, automaticity may be suppressed and phase 4 depolarization eliminated.

It is difficult to suggest a mechanism for lidocaine's antiarrhythmic action on the basis of its effects on normal ventricular myocardial tissue and His-Purkinje tissue.

Electrocardiographic Changes

Lidocaine does not usually change the PR, QRS, or QT interval, although the QT may be shortened in some patients. The paucity of electrocardiographic changes reflects lidocaine's lack of effect on healthy myocardium and conducting tissue.

Hemodynamic Effects

Lidocaine does not depress myocardial function, even in the face of congestive heart failure, at usual doses.

Pharmacokinetics

The pharmacokinetic characteristics of lidocaine:

Oral bioavailability	30–40%
Onset of action	5–15 minutes intramuscularly (IM); immediate intravenously (IV)
Peak response	Unknown
Duration of action	60–90 minutes IM; 10–20 minutes IV
Plasma half-life	1–2 hours
Primary route of metabolism	90% hepatic
Primary route of excretion	10% renal (unchanged), remainder as metabolites
Therapeutic serum concentration	1.5–5.0 μg/mL

Clinical Uses

Lidocaine is useful in the control of ventricular arrhythmias, particularly in patients with acute myocardial infarction. Lidocaine is the drug of choice for treatment of the electrical manifestations of digitalis intoxication.

Adverse Effects

The most common toxic reactions seen after lidocaine administration affect the CNS. Drowsiness is common, but unless excessive may not be particularly undesirable in patients with acute myocardial infarction. Some patients have paresthesias, disorientation, and muscle twitching that may forewarn of more serious deleterious effects, including psychosis, respiratory depression, and seizures.

Lidocaine may produce clinically significant hypotension, but this is exceedingly uncommon if the drug is given in moderate dosage. Depression of an already damaged myocardium may result from large doses.

Contraindications

Contraindications include hypersensitivity to local anesthetics of the amide type (a very rare occurrence), severe hepatic dysfunction, a history of grand mal seizures due to lidocaine, and age 70 or older. Lidocaine is contraindicated in the presence of second- or third-degree heart block, since it may increase the degree of block and can abolish the idioventricular pacemaker responsible for maintaining the cardiac rhythm.

Drug Interactions

The concurrent administration of lidocaine with cimetidine but not ranitidine may cause an increase (15%) in the plasma concentration of lidocaine. This effect is a manifestation of cimetidine reducing the clearance and volume of distribution of lidocaine. The myocardial depressant effect of lidocaine is enhanced by phenytoin administration.

Phenytoin

Phenytoin (*Dilantin*) was originally introduced for the control of convulsive disorders (see Chapter 32) but has now also been shown to be effective in the treatment of cardiac arrhythmias. Phenytoin appears to be particularly effective in treating ventricular arrhythmias in children.

Electrophysiological Actions

Sinoatrial Node

Most clinically used concentrations of phenytoin do not significantly alter sinus rate in humans. However, the hypotension that may follow IV administration of phenytoin can result in an increase in sympathetic tone and therefore an increased sinus heart rate.

Atrium

Phenytoin, like lidocaine, usually does not alter the action potential duration or ERP of atrial tissue except at very high concentrations. Atrial conduction velocity is either unchanged or slightly depressed.

A-V Node

Phenytoin lacks the anticholinergic properties of quinidine, disopyramide, and procainamide. However, the direct actions of phenytoin on the A-V node facilitate transmission.

His-Purkinje System

The electrophysiological effects of phenytoin on the His-Purkinje system resemble those of lidocaine; that is,

action potential duration and ERPs are shortened. Phenytoin decreases the rate of phase 4 depolarization in Purkinje tissue and reduces the rate of discharge of ventricular pacemakers.

Electrocardiographic Changes

Because phenytoin improves A-V conduction and shortens the action potential duration of ventricular myocardium, it may decrease the PR and QT intervals of the surface electrocardiogram.

Hemodynamic Effects

The effects of phenytoin on the cardiovascular system vary with the dose, the mode and rate of administration, and any cardiovascular pathology. Rapid administration can produce transient hypotension that is the combined result of peripheral vasodilation and depression of myocardial contractility. These effects are due to direct actions of phenytoin on the vascular bed and ventricular myocardium. If large doses are given slowly, dose-related decreases in left ventricular force, rate of force development, and cardiac output can be observed, along with an increase in left ventricular end-diastolic pressure.

Pharmacokinetics

The pharmacokinetic characteristics of phenytoin:

Oral bioavailability	Slow and variable
Onset of action	1–2 hours
Peak response	1.5–6 hours
Duration of action	Variable
Plasma half-life	22 hours
Primary route of metabolism	Hepatic
Primary route of excretion	5% renal (unchanged); remainder as metabolites
Therapeutic serum concentration	10–18 μg/mL

Clinical Uses

Phenytoin, like lidocaine, is more effective in the treatment of ventricular than supraventricular arrhythmias. It is particularly effective in treating ventricular arrhythmias associated with digitalis toxicity, acute myocardial infarction, open-heart surgery, anesthesia, cardiac catheterization, cardioversion, and angiographic studies.

Phenytoin finds its most effective use in the treatment of supraventricular and ventricular arrhythmias associated with digitalis intoxication. The ability of phenytoin to improve digitalis-induced depression of A-V conduction is a special feature that contrasts with the actions of other antiarrhythmic agents.

Adverse Effects

The rapid IV administration of phenytoin can present a hazard. Respiratory arrest, arrhythmias, and hypotension have been reported. Other adverse reactions and potential drug interactions are discussed in Chapter 32.

Contraindications

Phenytoin either should not be used or should be used cautiously in patients with hypotension, severe bradycardia, high-grade A-V block, severe heart failure, or hypersensitivity to the drug.

Because of the increase in A-V transmission observed with phenytoin administration, it should not be given to patients with atrial flutter or atrial fibrillation. Phenytoin will probably not restore normal sinus rhythm and may dangerously accelerate the ventricular rate.

Drug Interactions

Plasma phenytoin concentrations are increased in the presence of chloramphenicol, disulfiram, and isoniazid, since the latter drugs inhibit the hepatic metabolism of phenytoin. A reduction in phenytoin dose can alleviate the consequences of these drug–drug interactions.

Tocainide

Tocainide (*Tonocard*) is an orally effective antiarrhythmic agent with close structural similarities to lidocaine.

Electrophysiological Actions

In healthy volunteers, tocainide produced a slight depression in His-Purkinje conduction as well as a slightly delayed enhancement of A-V node conduction during atrial pacing. No significant alterations in heart rate, right ventricular ERP or the excitation thresholds of atrial or ventricular muscle were observed in these subjects.

Hemodynamic Effects

The acute hemodynamic effects are slight and transient and are observed most often during or immediately after drug infusion.

Pharmacokinetics

The pharmacokinetic characteristics of tocainide:

Oral bioavailability	Approximately 100%
Onset of action	Not known
Peak response	0.5–2 hours
Duration of action	8 hours
Plasma half-life	15 hours

Primary route of metabolism	Hepatic
Primary route of excretion	Renal (40% unchanged)
Therapeutic serum	3–11 μg /mL concentration

Clinical Uses

Tocainide is indicated for the treatment of symptomatic ventricular arrhythmias refractory to more conventional therapy. Serious noncardiac adverse effects limit its use to patients with life-threatening arrhythmias.

Adverse Effects

Light-headedness, dizziness, or nausea occurs in approximately 15% of patients, paresthesias and numbness in 9%, and tremor in 8%. These adverse effects are generally mild in intensity, transient, and dose related. Overall, however, approximately 20% of patients prescribed tocainide discontinue therapy because of such effects. Serious immune-based side effects, such as pulmonary fibrosis, have been reported, and blood dyscrasias, such as agranulocytosis and thrombocytopenia, may occur in up to 0.2% of patients.

Contraindications

Patients who are hypersensitive to tocainide or to local anesthetics of the amide type should not be exposed to tocainide. The presence of second- or third-degree heart block in the absence of an artificial pacemaker also contraindicates the use of tocainide.

Drug Interactions

When used with other class IB antiarrhythmic drugs, tocainide toxicity may be increased without significant gain in antiarrhythmic efficacy.

Mexiletine

Mexiletine (*Mexitil*) is an antiarrhythmic agent with pharmacological and antiarrhythmic properties similar to those of lidocaine and tocainide. Like tocainide, mexiletine is available for oral administration.

Electrophysiological Actions

As with other members of class IB, mexiletine slows the maximal rate of depolarization of the cardiac membrane action potential and exerts a negligible effect on repolarization. Mexiletine demonstrates a rate-dependent blocking action on the sodium channel, with rapid onset and recovery kinetics suggesting that it may be more useful for the control of rapid as opposed to slow ventricular tachyarrhythmias.

Hemodynamic Effects

Although its cardiovascular toxicity is minimal, mexiletine should be used with caution in patients who are hypotensive or who exhibit severe left ventricular dysfunction.

Pharmacokinetics

The pharmacokinetic characteristics of mexiletine:

Oral bioavailability	90%
Onset of action	0.5–2 hours
Peak response	2–3 hours
Duration of action	8–12 hours
Plasma half-life	10–12 hours
Primary route of metabolism	Hepatic
Primary route of excretion	Primarily biliary; 10% renal
Therapeutic serum concentration	0.5–2 μg /mL

Clinical Uses

Mexiletine is useful as an antiarrhythmic agent in the management of patients with either acute or chronic ventricular arrhythmias. While it is not at present an indication for use, there is interest in using mexiletine to treat the congenital long QT syndrome when an abnormality in the SCN5A gene (LQTS 3) has been found.

Adverse Effects

A very narrow therapeutic window limits mexiletine use. The first signs of toxicity manifest as fine tremor of the hands, followed by dizziness and blurred vision. Hypotension, sinus bradycardia, and widening of the QRS complex have been noted as the most common unwanted cardiovascular effects of IV mexiletine. The side effects of oral maintenance therapy include reversible upper gastrointestinal distress, tremor, lightheadedness, and coordination difficulties. These effects generally are not serious and can be reduced by downward dose adjustment or administering the drug with meals. Cardiovascular adverse effects, which are less common, include palpitations, chest pain, and angina or anginalike pain.

Contraindications

Mexiletine is contraindicated in the presence of cardiogenic shock or preexisting second- or third-degree heart block in the absence of a cardiac pacemaker. Caution must be exercised in administration of the drug to patients with sinus node dysfunction or disturbances of intraventricular conduction.

Drug Interactions

An upward adjustment in dose may be required when mexiletine is administered with phenytoin or rifampin, since these drugs stimulate the hepatic metabolism of mexiletine, reducing its plasma concentration.

CLASS IC

Flecainide

Flecainide (*Tambocor*) is a fluorinated aromatic hydrocarbon examined initially for its local anesthetic action and subsequently found to have antiarrhythmic effects. Flecainide inhibits the sodium channel, leading to conduction slowing in all parts of the heart, but most notably in the His-Purkinje system and ventricular myocardium. It has relatively minor effects on repolarization. Flecainide also inhibits abnormal automaticity.

Electrophysiological Actions

Sinoatrial Node

Flecainide decreases the sinus cycle length but results in a clinically insignificant decrease in heart rate.

Atrium

Flecainide decreases the maximal rate of depolarization in atrial tissue and shifts the membrane responsiveness curve to the right.

A-V Node

The atrioventricular conduction time, measured as the A–H interval, is prolonged by flecainide as is the His-Purkinje or H–V interval.

His-Purkinje System and Ventricular Muscle

Flecainide slows conduction in the His-Purkinje system and ventricular muscle to a greater degree than in the atrium. Flecainide may also cause block in accessory A-V connections, which is the principal mechanism for its effectiveness in treating A-V reentrant tachycardia.

Electrocardiographic Changes

Flecainide increases the PR, QRS, and to a lesser extent, QTc intervals. The rate of ventricular repolarization is not affected, and the QT interval prolongation is caused by the increase in the QRS duration.

Hemodynamic Effects

Flecainide produces modest negative inotropic effects that may become significant in the subset of patients with compromised left ventricular function.

Pharmacokinetics

The pharmacokinetic characteristics of flecainide:

Oral bioavailability	85–90%
Onset of action	1–2 hours
Peak response	1.5–6 hours
Duration of action	1–2 days
Plasma half-life	12–30 hours
Primary route of metabolism	Hepatic
Primary route of excretion	10–50% renal; 5% fecal
Therapeutic serum concentration	0.2–1.0 μg /mL

Clinical Uses

Flecainide is effective in treating most types of atrial arrhythmias. It is also used for life-threatening ventricular arrhythmias. However, flecainide should be used with extreme caution in any patient with structural heart disease. Flecainide crosses the placenta, with fetal levels reaching approximately 70% of maternal levels. In many centers, it is the second-line drug after digoxin for therapy of fetal arrhythmias. Because of the high incidence of proarrhythmia, initiation of therapy or significant increases in dosing should be performed only on inpatients.

Adverse Effects

Most adverse effects occur within a few days of initial drug administration. The most frequently reported effects are dizziness, light-headedness, faintness, unsteadiness, visual disturbances, blurred vision (e.g., spots before the eyes, difficulty in focusing), nausea, headache, and dyspnea.

Worsening of heart failure and prolongation of the PR and QRS intervals are likely to occur with flecainide, and an increased risk of proarrhythmia has been reported.

Contraindications

Flecainide is contraindicated in patients with preexisting second- or third-degree heart block or with bundle branch block unless a pacemaker is present to maintain ventricular rhythm. It should not be used in patients with cardiogenic shock.

Drug Interactions

In patients whose condition has been stabilized by flecainide, the addition of cimetidine may reduce the rate of flecainide's hepatic metabolism, increasing the potential for toxicity. Flecainide may increase digoxin concentrations on concurrent administration.

Propafenone

Propafenone (*Rythmol*) exhibits predominantly class IC properties with conduction slowing due to sodium

channel blockade. Additionally, propafenone is a weak β-receptor and L-type calcium channel blocker.

Electrophysiological Actions

As with all members of its class, propafenone has its major effect on the fast inward sodium current. The IC agents depress V_{max} over a wide range of heart rates and shift the resting membrane potential in the direction of hyperpolarization. The IC agents bind slowly to the sodium channel and dissociate slowly. Therefore, they exhibit rate-dependent block. Inhibition of the sodium channel throughout the cardiac cycle will result in a decrease in the rate of ectopy and trigger ventricular tachycardia.

Sinoatrial Node

Propafenone causes sinus node slowing that could lead to sinoatrial block. It may lengthen the sinus node recovery time with minimal effects on sinus cycle length.

Atrium

The action potential duration and ERP of atrial muscle are both prolonged by propafenone. The electrophysiological effects persist beyond removal of the drug from the tissue. In patients with atrial flutter, fibrillation, or tachycardia, propafenone can slow the atrial rate, resulting in a change from 2:1 or 4:1 A-V block to 1:1 A-V conduction with a subsequent increase in the ventricular rate.

A-V Node

The IV administration of propafenone slows conduction through the A-V node.

His-Purkinje System and Ventricular Muscle

Propafenone slows conduction and inhibits automatic foci.

Electrocardiographic Changes

Propafenone causes dose-dependent increases in the PR and QRS intervals.

Hemodynamic Effects

The IV administration of propafenone is accompanied by an increase in right atrial, pulmonary arterial, and pulmonary artery wedge pressures in addition to an increase in vascular resistance and a decrease in the cardiac index. A significant decrease in ejection fraction may be observed in patients with preexisting left ventricular dysfunction. In the absence of cardiac abnormalities, propafenone has no significant effects on cardiac function.

Pharmacokinetics

The pharmacokinetic characteristics of propafenone:

Oral bioavailability	Nearly complete
Onset of action	1 hour
Peak response	2–3 hours
Duration of action	8–12 hours
Plasma half-life	2–10 hours
Primary route of metabolism	Hepatic
Primary route of excretion	18.5–38% renal (unchanged)
Therapeutic serum concentration	<1 μ/mL

Clinical Uses

Approved indications for propafenone include treatment of supraventricular arrhythmias and life-threatening ventricular arrhythmias in the absence of structural heart disease. Propafenone has been shown to increase mortality in patients with structural heart disease, and so extreme caution must be used in this subset of patients. As with flecainide, the patient should be hospitalized for initiation of therapy.

Adverse Effects and Drug Interactions

Concurrent administration of propafenone with digoxin, warfarin, propranolol, or metoprolol increases the serum concentrations of the latter four drugs. Cimetidine slightly increases the propafenone serum concentrations. Additive pharmacological effects can occur when lidocaine, procainamide, and quinidine are combined with propafenone.

As with other members of class IC, propafenone may interact in an unfavorable way with other agents that depress A-V nodal function, intraventricular conduction, or myocardial contractility.

Overall, 21 to 32% of patients have adverse effects. The most common are dizziness or light-headedness, metallic taste, nausea, and vomiting; the most serious are proarrhythmic events.

Contraindications

Propafenone is contraindicated in the presence of severe or uncontrolled congestive heart failure; cardiogenic shock; sinoatrial, A-V, and intraventricular disorders of conduction; and sinus node dysfunction, such as sick sinus syndrome. Other contraindications include severe bradycardia, hypotension, obstructive pulmonary disease, and hepatic and renal failure. Because of its weak β-blocking action, propafenone may cause possible dose-related bronchospasm. This problem is greatest in patients who are slow metabolizers.

CLASS II

Table 16.3 summarizes the cardiac electrophysiological effects of class II, III, and IV agents, and Table 16.4 summarizes the actions of the β-receptor blocking agents

TABLE 16.3 Cardiac Electrophysiological Effects of Class II–IV Antiarrhythmic Drugs

		Conduction Velocity						
Drug	**Class**	**SA Node[a]**	**Atria**	**A-V Node**	**His-Purkinje**	**Ventricular Muscle**	**APD Atria/ Ventricle**	**ERP Atria/Ventricle**
Propranolol	II	D	D	D	–	–	–	–
Acebutolol	II	D	D	D	–	–	–	–
Esmolol	II	D	D	D	–	–	–	–
Sotalol	II/III	D	–	D	–	–	Increase[b]	Increase
Bretylium	III	I/D	–	I/D	–	–	Increase	Decrease Increase
Dofetilide	III	–	–	–	–	–	Increase[b]	Increase
Ibutilide	III	D±	–	D±	–	–	Increase[b]	Increase
Amiodarone	III	D	D	D	–	–	Increase[b]	Increase
Verapamil	IV	D	–	D	–	–	Decrease	–
Diltiazem	IV	D	–	D	–	–	Decrease	–

a*Spontaneous phase 4 depolarization.*
[b] *Increase in the QTc interval.*
SA, sinoatrial; D, decrease in conduction velocity; I , increase in conduction velocity; –, no significant effect with clinically relevant doses; ±, minimal effect.

that make up the class II drugs. Bear in mind the complete spectrum of cardiovascular effects of these agents when prescribing their use. For example, while patients with a normally functioning cardiovascular system may tolerate adrenergic blockade of the heart, patients with compensated heart failure, who depend on adrenergic tone to maintain an adequate cardiac output, may undergo acute congestive heart failure if prescribed any of the class II drugs. Table 16.5 summarizes the clinical use of the β-adrenoceptor blocking drugs in the treatment of cardiac arrhythmias.

Propranolol

Propranolol (*Inderal*) is the prototype β-blocker (see Chapter 11). It decreases the effects of sympathetic stimulation by competitive binding to β-adrenoceptors.

Electrophysiological Actions

Propranolol has two separate and distinct effects. The first is a consequence of the drug's β-blocking properties and the subsequent removal of adrenergic influences on the heart. The second is associated with its direct myocardial effects (membrane stabilization). The latter action, especially at high clinically employed doses, may account for its effectiveness against arrhythmias in which enhanced β-receptor stimulation does not play a significant role in the genesis of the rhythm disturbance.

Sinoatrial Node

Propranolol slows the spontaneous firing rate of nodal cells by decreasing the slope of phase 4 depolarization.

Atrium

Propranolol has local anesthetic properties and exerts actions similar to those of quinidine on the atrial membrane action potential. Membrane responsiveness and action potential amplitude are reduced, and excitability is decreased; conduction velocity is reduced. Because these concentrations are similar to those that produce β-blockade, it is impossible to determine whether the drug acts by specific receptor blockade or via a membrane-stabilizing effect.

A-V Node

The depressant effects of propranolol on the A-V node are more pronounced than are the direct depressant effects of quinidine. This is due to propranolol's dual actions of β-blockade and direct myocardial depression. Propranolol administration results in a decrease in A-V conduction velocity and an increase in the A-V nodal refractory period. Propranolol does not display the anticholinergic actions of quinidine and other antiarrhythmic agents.

His-Purkinje System and Ventricular Muscle

Propranolol decreases Purkinje fiber membrane responsiveness and reduces action potential amplitude. His-Purkinje tissue excitability also is reduced. These changes result in a decrease in His-Purkinje conduction velocity. However, these electrophysiological alterations are observed at propranolol concentrations in excess of those normally used in therapy. The most striking electrophysiological property of propranolol at usual therapeutic concentrations is a depression of catecholamine-stimulated automaticity.

TABLE 16.4 General Clinical Uses of Individual Antiarrhythmic Drugs

Drugs	Therapeutic Uses
Acebutolol	Ventricular arrhythmias, ventricular ectopy
Adenosine	Supraventricular tachycardia Wolff-Parkinson-White syndrome
Amiodarone	Hemodynamically unstable ventricular tachycardia Ventricular fibrillation
Bretylium	Ventricular arrhythmias after cardiac surgery Ventricular fibrillation
Diltiazem	Paroxysmal supraventricular tachycardia Atrial fibrillation
Disopyramide	Premature ventricular contractions Atrial arrhythmias, episodic ventricular tachycardia
Dofetilide	Atrial fibrillation and flutter
Esmolol	Atrial fibrillation and flutter, automatic tachycardias
Flecainide	Ventricular tachycardia
Ibutilide	Atrial fibrillation and flutter
Lidocaine	Post–myocardial infarct arrhythmias Ventricular tachycardia
Magnesium sulfate	Sustained ventricular arrhythmias Torsades de pointes of magnesium depletion or glycoside toxicity
Mexiletine	Premature ventricular contractions Ventricular tachycardia
Moricizine	Ventricular tachycardia
Phenytoin	Digitalis-induced cardiac arrhythmias
Procainamide	Atrial tachycardia, ventricular tachycardia Premature ventricular contractions
Propafenone	Atrial fibrillation, ventricular tachycardia Premature ventricular contractions
Propranolol	Supraventricular arrhythmias Postoperative ventricular arrhythmias Wolff-Parkinson-White syndrome
Quinidine	Atrial arrhythmias, ventricular tachycardia
Sotalol	Ventricular arrhythmias, ventricular fibrillation
Tocainide	Premature ventricular contractions Ventricular tachycardia
Verapamil	Paroxysmal supraventricular tachycardia Atrial fibrillation

Electrocardiographic Changes

Propranolol prolongs the PR interval but does not change the QRS interval. It may shorten the QT interval.

Hemodynamic Effects

The blockade of cardiac β-adrenoceptors prevents or reduces the usual positive inotropic and chronotropic actions of catecholamine administration on cardiac sympathetic nerve stimulation. Blockade of β-receptors prolongs systolic ejection periods at rest and during exercise. Both alterations tend to increase myocardial oxygen consumption. However, these alterations are offset by factors that tend to reduce oxygen consumption, such as decreased heart rate and decreased force of contraction. The decrease in oxygen demand produced by a decrease in heart rate and a decrease in force of contraction is usually greater than the increase in oxygen demand that results from increased heart size and increased ejection time. The net result is that oxygen demand is decreased.

Pharmacokinetics

The pharmacokinetic characteristics of propranolol:

Oral bioavailability	30–40%
Onset of action	1–2 hours
Peak response	1.0–1.5 hours
Duration of action	6–24 hours
Plasma half-life	3–5 hours
Primary route of metabolism	Hepatic
Primary route of excretion	Renal
Therapeutic serum concentration	0.02–1 μg /mL

Clinical Uses

Propranolol is indicated in the management of a variety of cardiac rhythm abnormalities that are totally or partially due to enhanced adrenergic stimulation. In selected cases of sinus tachycardia caused by anxiety, pheochromocytoma, or thyrotoxicosis, β-blockade will reduce the spontaneous heart rate.

Propranolol alone or in conjunction with digitalis can help control the ventricular rate in patients with atrial flutter or atrial fibrillation. Patients with supraventricular extrasystoles and intermittent paroxysms of atrial fibrillation may benefit from β-receptor blockade with propranolol.

The arrhythmias associated with halothane or cyclopropane anesthesia have been attributed to the interaction of the anesthetic with catecholamines, and they have been suppressed by IV administration of 1 to 3 mg propranolol. An increase in circulating catecholamines also has been observed in patients with acute myocardial infarction and has been correlated with the development of arrhythmias.

Clinically, tachyarrhythmias associated with digitalis excess (including supraventricular and ventricular extrasystoles) and ventricular tachycardia have been suppressed by propranolol. Although propranolol is highly effective in the treatment of digitalis-induced arrhythmias, phenytoin and lidocaine are preferred.

Long-term treatment with β-adrenoceptor blocking agents is clearly associated with an increased rate of

TABLE 16.5 Efficacy of β-Adrenoceptor Blocking Agents in the Control of Cardiac Rhythm Disorders

Rhythm Disorder	Efficacy of β-Adrenoceptor Blocking Agent
Supraventricular arrhythmias	
Sinus tachycardia	First treat the underlying cause, e.g., hyperpyrexia, hypovolemia. β-Adrenoceptor blockade is most effective in decreasing the heart rate by inhibiting SA response to enhanced adrenergic stimulation. Do not use as the initial drug in tachycardia associated with pheochromocytoma.
Atrial fibrillation	Sinus rhythm is unlikely to be restored. However, the effect of β-adrenoceptor blockade on the A-V node will decrease the ventricular response to the atrial tachyarrhythmia. Effect is enhanced by the simultaneous use of digoxin or verapamil.
Atrial flutter/tachycardia	*β*-Adrenoceptor blockers will reduce the ventricular rate by inhibition of transmission through the A-V node as a result of inhibition of adrenergic influences. May be useful for the prevention of recurrent episodes of tachyarrhythmia.
Ventricular arrhythmias	
Premature ventricular complexes	Effective in mitral valve prolapse, hypertrophic cardiomyopathy, digitalis-related ectopic activity, and ventricular complexes associated with exercise or induced by ischemia.
Ventricular tachycardia	Most effective against arrhythmias associated with digitalis toxicity and exercise, particularly if the latter is related to ischemia.
Ventricular fibrillation	Postmyocardial infarct patients show increased survival if treated with a β-adrenoceptor antagonist. The beneficial effect may be related to the decrease in heart rate and the antiischemic benefits of β-adrenoceptor blockade.

SA, sinoatrial.

survival in patients with ischemic heart disease who have recovered from an acute myocardial infarction. Propranolol is the drug of choice for treating patients with the congenital long QT syndrome.

Adverse Effects

The toxicity associated with propranolol is for the most part related to its primary pharmacological action, inhibition of the cardiac β-adrenoceptors. This topic is discussed in detail in Chapter 11. In addition, propranolol exerts direct cardiac depressant effects that become manifest when the drug is administered rapidly by the IV route. Glucagon immediately reverses all cardiac depressant effects of propranolol, and its use is associated with a minimum of side effects. The inotropic agents amrinone (*Inocor*) and milrinone (*Primacor*) provide alternative means of augmenting cardiac contractile function in the presence of β-adrenoceptor blockade (see Chapter 15). Propranolol may also stimulate bronchospasm in patients with asthma.

Since propranolol crosses the placenta and enters the fetal circulation, fetal cardiac responses to the stresses of labor and delivery will be blocked. Additionally, propranolol crosses the blood-brain barrier and is associated with mood changes and depression. School difficulties are commonly associated with its use in children. Propranolol may also cause hypoglycemia in infants.

Contraindications

Propranolol is contraindicated for patients with depressed myocardial function and may be contraindicated in the presence of digitalis toxicity because of the possibility of producing complete A-V block and ventricular asystole. Patients receiving anesthetic agents that tend to depress myocardial contractility (ether, halothane) should not receive propranolol. Propranolol should be used with extreme caution in patients with asthma.

Up-regulation of β-receptors follows long-term therapy, making abrupt withdrawal of β-blockers dangerous for patients with ischemic heart disease.

Acebutolol

Acebutolol (*Sectral*) is a cardioselective β_1-adrenoceptor blocking agent that also has some minor membrane stabilizing effects on the action potential.

Electrophysiological Actions

Acebutolol's effects on the atria, sinoatrial and AV nodes, His-Purkinje system, and ventricular muscle are similar to those of propranolol.

Hemodynamic Effects

Acebutolol reduces blood pressure in patients with essential hypertension primarily through its negative inotropic and chronotropic effects.

Pharmacokinetics

The pharmacokinetic characteristics of acebutolol:

Oral bioavailability	70%
Onset of action	1–3 hours

Peak response	3–8 hours
Duration of action	12–24 hours
Plasma half-life	3–4 hours
Primary route of metabolism	Hepatic
Primary route of excretion	Renal (30–40%); biliary/fecal (50–60%)
Therapeutic serum concentration	Not established

Clinical Uses

Acebutolol is effective in the management of the patient with essential hypertension, angina pectoris, and ventricular arrhythmias. Antiarrhythmic effects are observed with the patient both at rest and taking exercise.

Adverse Effects

Adverse effects include bradycardia, gastrointestinal upset, dizziness, and headache.

Contraindications

Acebutolol should not be administered in cardiogenic shock, uncontrolled heart failure, or severe bradycardia or to patients with known hypersensitivity to the drug.

Esmolol

Esmolol (*Brevibloc*) is a short-acting intravenously administered β_1-selective adrenoceptor blocking agent. It does not possess membrane-stabilizing activity or sympathomimetic activity.

Electrophysiological Actions

Esmolol's electrophysiological actions are similar to those of propranolol.

Hemodynamic Effects

Esmolol decreases arterial pressure, heart rate, ventricular contractility, and pulmonary vascular resistance.

Pharmacokinetics

The pharmacokinetic characteristics of esmolol:

Oral bioavailability	100%
Onset of action	15–30 minutes
Peak response	2–5 minutes
Duration of action	20–30 minutes
Plasma half-life	3.7 hours
Primary route of metabolism	Hepatic
Primary route of excretion	Renal
Therapeutic serum concentration	0.4–1.2 μg /mL

Clinical Uses

Esmolol is used in the treatment of supraventricular tachyarrhythmias for rapid control of ventricular rate and reduction of myocardial oxygen consumption. Discontinuation of administration is followed by a rapid reversal of its pharmacological effects because of esmolol's rapid hydrolysis by plasma esterases.

Adverse Effects and Contraindications

The most frequently reported adverse effects are hypotension, nausea, dizziness, headache, and dyspnea. As with many β-blocking drugs, esmolol is contraindicated in patients with overt heart failure and those in cardiogenic shock.

CLASS III

Bretylium

Bretylium (*Bretylol*) was introduced for the treatment of essential hypertension but subsequently was shown to suppress the ventricular fibrillation often associated with acute myocardial infarction.

Electrophysiological Actions

The net effects of bretylium on the electrical and mechanical properties of the heart are a composite of the direct actions of the drug on cardiac tissues and indirect actions mediated through the drug's effects on the sympathetic nervous system.

Sinoatrial Node

Bretylium administration produces an initial brief increase in sinus node automaticity that is probably the result of a drug-induced release of catecholamines from sympathetic nerve terminals. No change or a slight decrease in sinus heart rate is observed after the initial phase of catecholamine release.

Atria

At therapeutic concentrations, the only significant effect of bretylium is to prolong the action potential. This results in prolongation of the ERP of the atrial muscle.

A-V Node

Moderate doses increase conduction velocity and decrease the A-V nodal refractory period; this effect may result from the initial drug-induced catecholamine release. The net effect of bretylium on A-V transmission during chronic therapy is unknown.

His-Purkinje System and Ventricular Muscle

The most prominent electrophysiological action of bretylium is to raise the intensity of electrical current

necessary to induce ventricular fibrillation. This action, which is more prominent with bretylium than with any other available antiarrhythmic agent, can be observed in both normal and ischemic hearts.

Hemodynamic Effects

A unique property of bretylium as an antiarrhythmic agent is its positive inotropic action. This effect, related to its actions on the sympathetic nervous system, includes an initial release of neuronal stores of norepinephrine followed shortly by a prolonged period of inhibition of direct or reflex-associated neuronal norepinephrine release. The onset of bretylium-induced hypotension is delayed 1 to 2 hours because the initial catecholamine release maintains arterial pressure before this time.

Pharmacokinetics

The pharmacokinetic characteristics of bretylium:

Oral bioavailability	Not applicable
Onset of action	5–10 mm
Peak response	6–9 hours (TM)
Duration of action	6–24 hours
Plasma half-life	6.9–8.1 hours
Primary route of metabolism	None
Primary route of excretion	Renal (unchanged)
Therapeutic serum concentration	0.5–2.5 μg /mL

Clinical Uses

Bretylium is not to be considered a first-line antiarrhythmic agent. However, because of its ability to prolong the refractory period of Purkinje fibers and to elevate the electrical threshold to ventricular fibrillation, *bretylium has been found useful in the treatment of life-threatening ventricular arrhythmias,* especially when conventional therapeutic agents, such as lidocaine or procainamide, prove to be ineffective. In addition, bretylium is known to facilitate the reversal of ventricular fibrillation by precordial electrical shock. Its use should be limited to no longer than 5 days.

Adverse Effects

The most important side effect associated with the use of bretylium is hypotension, a result of peripheral vasodilation caused by adrenergic neuronal blockade (a guanethidinelike action). Nausea, vomiting, and diarrhea have been reported with IV administration and can be minimized by slow infusion. Longer-term problems include swelling and tenderness of the parotid gland, particularly at mealtime.

Contraindications

The associated initial release of catecholamines may result in an excessive pressor response and stimulation of cardiac force and pacemaker activity. The resulting increase in myocardial oxygen consumption in a patient with ischemic heart disease may lead to ischemic pain (angina pectoris). Patients in a state of circulatory shock probably should not be administered bretylium because of its delayed sympatholytic action.

Amiodarone

Amiodarone (*Cordarone*) is an iodine-containing benzofuran derivative identified as a class III agent because it predominantly prolongs action potentials. Amiodarone also blocks sodium and calcium channels and is a noncompetitive β-receptor blocker. Amiodarone is effective for the treatment of most arrhythmias. Toxicity associated with amiodarone has led the U. S. Food and Drug Administration (FDA) to recommend that it be reserved for use in patients with life-threatening arrhythmias.

Electrophysiological Actions

The most notable electrophysiological effect of amiodarone after long-term administration is prolongation of repolarization and refractoriness in all cardiac tissues, an action that is characteristic of class III antiarrhythmic agents.

Sinoatrial Node

Amiodarone decreases the slope of phase 4 depolarization. The rate of spontaneous discharge of the sinoatrial node is increased by amiodarone as well as by its metabolite, desethylamiodarone. The depressant action of amiodarone on sinoatrial pacemaker function is, in addition to β-receptor blockade, related to an inhibition of the slow inward current carried by the calcium ion.

Amiodarone prolongs the action potential in atrial muscle and increases the absolute and effective refractory periods.

Amiodarone, like its major metabolite desethylamiodarone, increases A-V nodal conduction time and refractory period.

His-Purkinje System and Ventricular Muscle

The dominant effect on ventricular myocardium that has been chronically exposed to either amiodarone or desethylamiodarone is a prolongation in the action potential with an associated increase in the refractory period and a modest decrease in V_{max} as a function of stimulus frequency. Amiodarone inhibits the delayed outward potassium current, a finding consistent with the observation of a prolonged action potential. Both amiodarone and its metabolite significantly decrease the ac-

tion potential duration and shorten the ERP in Purkinje fibers, at the same time prolonging action potential in ventricular muscle.

Electrocardiographic Changes

Amiodarone's predominant electrocardiographic changes include prolongation of the PR and QT intervals, development of U waves, and changes in T-wave contour.

Hemodynamic Effects

Amiodarone relaxes vascular smooth muscle; one of its most prominent effects is on the coronary circulation, reducing coronary vascular resistance and improving regional myocardial blood flow. In addition, its effects on the peripheral vascular bed lead to a decrease in left ventricular stroke work and myocardial oxygen consumption. Therefore, amiodarone improves the relationship between myocardial oxygen demand and oxygen supply. IV administration may be associated with profound hypotension requiring volume expansion therapy.

Pharmacokinetics

The pharmacokinetic characteristics of amiodarone are extremely complex:

Oral bioavailability	35–65%
Onset of action	2–3 days, up to 2–3 months
Peak response	3–7 hours after IV administration
Duration of action	Variable, weeks to months
Plasma half-life	2–10 days; 26–107 days with chronic administration
Primary route of metabolism	Hepatic, active metabolites
Primary route of excretion	Biliary
Therapeutic serum concentration	0.5–2 μg /mL

Clinical Uses

Amiodarone is regarded as one of the most efficacious antiarrhythmic agents because of its usefulness in the management of a variety of cardiac rhythm disorders with minimal tendency for induction of torsades de pointes tachyarrhythmia. Its use, however, is limited by the multiple and severe noncardiac side effects that it produces.

Amiodarone is available as an IV formulation as well as an oral preparation. IV amiodarone is indicated for initiating treatment and for prophylaxis of frequently recurring ventricular fibrillation and hemodynamically unstable ventricular tachycardia in patients refractory to other therapy. IV administration also can be used to treat patients with ventricular tachycardia or ventricular fibrillation for whom oral amiodarone is indicated, but who are unable to take oral medication.

Amiodarone may elicit life-threatening side effects in addition to presenting substantial management difficulties associated with its use. The oral formulation of amiodarone is indicated only for the treatment of life-threatening recurrent ventricular arrhythmias (e.g., recurrent ventricular fibrillation and/or recurrent hemodynamically unstable ventricular tachycardia) that have not responded to other potentially effective antiarrhythmic drugs or when alternative interventions could not be tolerated. Despite its efficacy as an antiarrhythmic agent, there is no evidence from clinical trials that the use of amiodarone favorably affects survival.

Initiation of treatment with amiodarone should be done in the hospital setting and only by physicians familiar with the management of patients with life-threatening arrhythmias; this is because of the life-threatening nature of the arrhythmias and the possibility of interactions with previous therapy and of exacerbation of the arrhythmia.

Amiodarone is effective in maintaining sinus rhythm in most patients with paroxysmal atrial fibrillation and in many patients with persistent atrial fibrillation. It is also effective in preventing recurrences of A-V nodal reentry and atrial tachyarrhythmias and in the prevention of reentrant rhythms and atrial fibrillation in patients with Wolff-Parkinson-White syndrome. Also, it is the most efficacious therapy for postoperative junctional ectopic tachycardia.

Adverse Effects

Amiodarone's most significant adverse effects include hepatitis, exacerbation of arrhythmias, worsening of congestive heart failure, thyroid dysfunction, and pulmonary fibrosis. Pulmonary fibrosis is frequently fatal and may not be reversed with discontinuation of the drug. Interestingly, despite significant prolongation of the QT interval, the risk of torsades de pointes is relatively low.

Patients with underlying sinus node dysfunction tend to have significant worsening of nodal function, frequently requiring pacemaker implantation. Corneal microdeposits develop in most adults receiving amiodarone. As many as 10% of patients complain of halos or blurred vision. The corneal microdeposits are reversible with stoppage of the drug.

Photosensitization occurs in 10% of patients. With continued treatment, the skin assumes a blue-gray coloration. The risk is increased in patients of fair complexion. The discoloration of the skin regresses slowly, if at all, after discontinuation of amiodarone.

Amiodarone inhibits the peripheral and possibly intrapituitary conversion of thyroxine (T_4) to triiodothyronine (T_3) by inhibiting 5′-deiodination. The serum concentration of T_4 is increased by a decrease in its clearance, and thyroid synthesis is increased by a reduced suppression of the pituitary thyrotropin T_3. The concentration of T_3 in the serum decreases, and reverse T_3 appears in increased amounts. Despite these changes, most patients appear to be maintained in an euthyroid state. Manifestations of both hypothyroidism and hyperthyroidism have been reported.

Tremors of the hands and sleep disturbances in the form of vivid dreams, nightmares, and insomnia have been reported in association with the use of amiodarone. Ataxia, staggering, and impaired walking have been noted. Peripheral sensory and motor neuropathy or severe proximal muscle weakness develops infrequently. Both neuropathic and myopathic changes are observed on biopsy. Neurological symptoms resolve or improve within several weeks of dosage reduction.

Contraindications

Amiodarone is contraindicated in patients with sick sinus syndrome and may cause severe bradycardia and second- and third-degree atrioventricular block. Amiodarone crosses the placenta and will affect the fetus, as evidenced by bradycardia and thyroid abnormalities. The drug is secreted in breast milk.

Drug Interactions

Amiodarone increases the hypoprothrombinemic response to warfarin (an oral anticoagulant) by reducing its metabolism. Patients receiving digoxin may undergo an increase in serum digoxin concentrations when amiodarone is added to the treatment regimen. Amiodarone interferes with hepatic and renal elimination of flecainide, phenytoin, and quinidine.

Sotalol

In addition to class III actions, sotalol (*Betapace*) possesses β-adrenoceptor blocking properties. The β-blocking effects are most evident at low doses, with action potential prolongation predominating at higher doses. The D-isomer of sotalol, which is devoid of β-blocking action, may increase mortality in post-infarcted patients.

Electrophysiological Actions

Sinoatrial Node and Atrium

Pacemaker activity in the sinoatrial node is decreased because of β-adrenoceptor blockade and a removal of sympathoadrenal influences on spontaneous diastolic depolarization. Sotalol increases the refractory period of atrial muscle.

A-V Node

Sotalol decreases conduction velocity and prolongs the ERP in the A-V node, an action held in common with other β_1-adrenoceptor blocking agents.

His-Purkinje System and Ventricular Muscle

The actions of sotalol on the delayed rectifier potassium current prolong the ERP in His-Purkinje tissue. As with other members of class III, the electrophysiological action of sotalol is characterized by prolongation of repolarization and an increase in the ERP of ventricular muscle.

Electrocardiographic Changes

Administration of sotalol is associated with dose- and concentration-dependent slowing of the heart rate and prolongation of the PR interval. The QRS duration is not affected with plasma concentrations within the therapeutic range. The corrected QT interval is prolonged as a result of the increase in the ERP of ventricular myocardium.

Hemodynamic Effects

The hemodynamic effects of sotalol are related to its β-adrenoceptor antagonist activity. Accordingly, decreases in resting heart rate and in exercise-induced tachycardia are seen in patients receiving sotalol. A modest reduction in systolic pressure and in cardiac output may occur. The reduction in cardiac output is a consequence of lowering the heart rate, since stroke volume is unaffected by sotalol treatment. In patients with normal ventricular function, cardiac output is maintained despite the decrease in heart rate because of the simultaneous increase in the stroke volume.

Pharmacokinetics

The pharmacokinetic characteristics of sotalol:

Oral bioavailability	50%o
Onset of action	0.5 hours
Peak response	1–2 hours
Duration of action	12–24 hours
Plasma half-life	4 hours
Primary route of metabolism	Hepatic (80%)
Primary route of excretion	Renal (20% unchanged); 40% metabolite
Therapeutic serum concentration	1–4 μg /mL

Clinical Uses

Sotalol possesses a broad spectrum of antiarrhythmic effects in ventricular and supraventricular arrhythmias. It has value in the management of patients with paroxys-

mal supraventricular arrhythmias, in terminating the reentrant arrhythmia in which the atrioventricular node serves as the reentrant pathway, and possibly in terminating supraventricular tachyarrhythmias associated with an accessory pathway.

Adverse Effects

Side effects of sotalol include those attributed to both β-adrenoceptor blockade and proarrhythmic effects. This arrhythmia is a serious threat, as it may lead to ventricular fibrillation. Adverse effects attributable to its β-blocker activity include fatigue, dyspnea, chest pain, headache, nausea, and vomiting.

Contraindications

The contraindications that apply to other β-adrenoceptor blocking agents also apply to sotalol. In addition, hypokalemia and drugs known to prolong the QT interval may be contraindicated, as they enhance the possibility of proarrhythmic events.

Drug Interactions

Drugs with inherent QT interval–prolonging activity (i.e., thiazide diuretics and terfenadine) may enhance the class III effects of sotalol.

Dofetilide

Dofetilide (*Tikosyn*) is a "pure" class III drug. It prolongs the cardiac action potential and the refractory period by selectively inhibiting the rapid component of the delayed rectifier potassium current (IKr).

Electrophysiological Actions

Dofetilide's mechanism of action involves blockade of the cardiac ion channel that carries the rapid component of the delayed rectifier potassium current, IKr. Dofetilide inhibits IKr with no significant effects on other repolarizing potassium currents (e.g., IKs, IK1) over a wide range of concentrations. At plasma concentrations within the therapeutic range, dofetilide has no effect on sodium channels or on either α_1- or β-adrenoceptors.

Dofetilide blocks IKr in all myocardial tissues. It blocks open channels, and its binding and release from the channels is voltage dependent. The effects of dofetilide are exaggerated when the extracellular potassium concentration is reduced, which is important, as many patients may be receiving diuretics concurrently. Conversely, hyperkalemia decreases the effects of dofetilide, which may limit its efficacy when local hyperkalemia occurs, such as during myocardial ischemia. Dofetilide demonstrates reverse use dependence, that is, less influence on the action potential at faster heart rates. This is likely due to a greater influence of other repolarizing currents such as the slowly activating component of the delayed rectifier current (IKs).

Sinoatrial Node

Dofetilide induces a minor slowing of the spontaneous discharge rate of the sinoatrial node via a reduction in the slope of the pacemaker potential and hyperpolarization of the maximum diastolic potential.

Atrium

Dofetilide prolongs the plateau phase of the action potential, thereby lengthening the refractory period of the myocardium. The effects on atrial tissue appear to be more profound than those observed in the ventricle. The reason for this is unclear. There is no effect on the voltage-gated sodium channel and as such no effect on the conduction velocity.

A-V Node

There is no effect on conduction through the A-V node.

His-Purkinje System and Ventricular Muscle

Dofetilide increases the ERP of ventricular myocytes and Purkinje fibers. The ERP-prolonging effect on the ventricular tissue is somewhat less than that in atrial tissue.

Electrocardiographic Changes

There are no changes in the PR or QRS intervals, which reflects a lack of effect on the conduction velocity. The QT interval is prolonged as a result of an increase in both the effective and functional refractory periods in the His-Purkinje system and the ventricles. The increase in the QT interval is directly related to the dofetilide dose and plasma concentration.

Hemodynamic Effects

Dofetilide does not significantly alter the mean arterial blood pressure, cardiac output, cardiac index, stroke volume index, or systemic vascular resistance. There is a slight increase in the delta pressure/delta time (dP/dt) of ventricular myocytes.

Pharmacokinetics

The pharmacokinetic characteristics of dofetilide are summarized below. Although the absorption of dofetilide is delayed by ingestion of food, the total bioavailability is not affected. Dosing requires adjustment in patients with renal insufficiency.

Oral bioavailability	>90%
Onset of action	0.5 hour

Peak response	23 hours
Duration of action	8–10 hours
Plasma half-life	7–10 hours
Primary route of metabolism	Hepatic (CYP3A4)
Primary route of excretion	Renal (80% unchanged; 20% metabolites)
Therapeutic serum concentration	Not established

Clinical Uses

Dofetilide is approved for the treatment of atrial fibrillation and atrial flutter. Because of the lack of significant hemodynamic effects, dofetilide may be useful in patients with CHF who are in need of therapy for supraventricular tachyarrhythmias. Dofetilide is not indicated for use in the setting of ventricular arrhythmias.

Adverse Effects

The incidence of noncardiac adverse events is not different from that of placebo in controlled clinical trials. The principal cardiac adverse effect is the risk of torsades de pointes due to QT prolongation. The risk is approximately 3%, and most cases are observed in the first 3 days of therapy. As such, initiation of therapy should be performed with the patient in hospital.

Contraindications

Contraindications include baseline prolongation of the QT interval, use of other QT-prolonging drugs; history of torsades de pointes; a creatinine clearance of less than 20 mL/minute; simultaneous use of verapamil, cimetidine, or ketoconazole; uncorrected hypokalemia or hypomagnesemia; and pregnancy or breast-feeding.

Drug Interactions

Verapamil increases serum dofetilide levels, as do drugs that inhibit cationic renal secretion, such as ketoconazole and cimetidine, raise serum levels.

Ibutilide Fumarate

Ibutilide (*Corvert*) is a structural analog of sotalol and produces cardiac electrophysiological effects similar to those of the antiarrhythmic agents in class III.

Electrophysiological Actions

Ibutilide prolongs action potential in isolated adult cardiac myocytes and increases both atrial and ventricular refractoriness *in vivo*. An additional action is blockade of outward potassium currents. Thus, ibutilide acts by blocking the rapid component of the delayed rectifier current (IKr) as well as by activation of a slow inward current carried predominantly by sodium.

Sinoatrial Node

Although there is evidence that ibutilide causes a modest slowing of the sinus rate, there is no significant change in heart rate.

Atrium

Ibutilide causes an increase in the atrial refractory period, an effect seen at rapid heart rates.

A-V Node

Ibutilide slows conduction through the A-V node; however, there is no change in the PR interval on ECG.

His-Purkinje System and Ventricular Muscle

Ibutilide increases the ERP of ventricular myocytes and Purkinje fibers but has no clinically significant effect on QRS duration.

Electrocardiographic Changes

There are no changes in the PR or QRS intervals, which reflects a lack of effect on the conduction velocity. Although there is no relationship between the plasma concentration of ibutilide and its antiarrhythmic effect, there is a dose-related prolongation of the QT interval. The maximum effect on the QT interval is a function of both the dose of ibutilide and the rate of infusion.

Hemodynamic Effects

Ibutilide has no significant effects on cardiac output, mean pulmonary arterial pressure, or pulmonary capillary wedge pressure in patients with or without compromised ventricular function.

Pharmacokinetics

The pharmacokinetic characteristics of ibutilide are summarized next. The pharmacokinetics are highly variable between patients. Because of extensive first-pass metabolism, ibutilide is not suitable for oral administration.

Oral bioavailability	>90%
Onset of action	Minutes
Peak response	Minutes
Plasma half-life	3–4 hours (range 2–12 hours)
Primary route of metabolism	Hepatic
Primary route of excretion	Renal
Therapeutic serum concentration	Not applicable

Clinical Uses

Ibutilide is approved for the chemical cardioversion of recent-onset atrial fibrillation and atrial flutter. Ibutilide appears to be more effective in terminating atrial flutter than atrial fibrillation. It can also lower the defibrilla-

tion threshold for atrial fibrillation resistant to chemical cardioversion.

Adverse Effects

The major adverse effect associated with the use of ibutilide is the risk of torsades de pointes due to QT prolongation. Other reported adverse cardiovascular events (all <2%) include hypotension and hypertension, bradycardia and tachycardia, and varying degrees of A-V block. The incidence of noncardiac adverse events with the exception of nausea does not differ from that of placebo.

Contraindications

Contraindications to the use of ibutilide include baseline prolongation of the QT interval, use of other QT-prolonging drugs, history of torsades de pointes, hypersensitivity to ibutilide, uncorrected hypokalemia or hypomagnesemia, and pregnancy or breast-feeding.

Drug Interactions

Ibutilide has significant drug interactions.

CLASS IV

Verapamil

Verapamil (*Isoptin, Covera*), in addition to its use as an antiarrhythmic agent, has been employed extensively in the management of variant (Prinzmetal's) angina and effort-induced angina pectoris (see Chapters 17 and 19). It selectively inhibits the voltage-gated calcium channel that is vital for action potential genesis in slow-response myocytes, such as those found in the sinoatrial and A-V nodes.

Electrophysiological Actions

Sinoatrial Node

Spontaneous phase 4 depolarization, a characteristic of normal sinoatrial nodal cells, relies on progressive inhibition of an outward potassium current and an increase in a slow inward current that is carried by Na^+ and Ca^{++} ions. Verapamil decreases the rate of rise and slope of the slow diastolic depolarization, the maximal diastolic potential, and the membrane potential at the peak of depolarization in the sinoatrial node.

Atrium

Verapamil fails to exert any significant electrophysiological effects on atrial muscle.

A-V Node

Verapamil impairs conduction through the A-V node and prolongs the A-V nodal refractory period at plasma concentrations that show no effect on the His-Purkinje system.

His-Purkinje System and Ventricular Muscle

The most important electrocardiographic change produced by verapamil is prolongation of the PR interval, a response consistent with the known effects of the drug on A-V nodal transmission. Verapamil has no effect on intraatrial and intraventricular conduction. The predominant electrophysiological effect is on A-V conduction proximal to the His bundle.

Hemodynamic Effects

Usual IV doses of verapamil are not associated with marked alterations in arterial blood pressure, peripheral vascular resistance, heart rate, left ventricular end-diastolic pressure, or contractility.

Pharmacokinetics

The pharmacokinetic characteristics of verapamil:

Oral bioavailability	20–35%
Onset of action	1–2 hours
Peak response	1–2 hours
Duration of action	8–10 hours
Plasma half-life	2.8–7.4 hours
Primary route of metabolism	Hepatic; active metabolite
Primary route of excretion	Renal (30% unchanged)
Therapeutic serum concentration	0.125–0.4 μg /mL

Clinical Uses

Verapamil is useful for slowing the ventricular response to atrial tachyarrhythmias, such as atrial flutter and fibrillation. Verapamil is also effective in arrhythmias supported by enhanced automaticity, such as ectopic atrial tachycardia and idiopathic left ventricular tachycardia.

Adverse Effects

Orally administered verapamil is well tolerated by most patients. Most complaints are of constipation and gastric discomfort. Other complaints include vertigo, headache, nervousness, and pruritus.

Contraindications

Verapamil must be used with extreme caution or not at all in patients who are receiving β-adrenoceptor blocking agents. Normally, the negative chronotropic effect of verapamil will in part be overcome by an increase in reflex sympathetic tone. The latter is be prevented by simultaneous administration of a β-adrenoceptor blocking agent, which exaggerates the depressant effects of

verapamil on heart rate, A-V node conduction, and myocardial contractility. The use of verapamil in children less than 1 year of age is controversial.

Diltiazem

The antiarrhythmic actions and uses of diltiazem (*Cardizem;* see Chapter 19) are similar to those of verapamil. *Diltiazem is effective in controlling the ventricular rate in patients with atrial flutter or atrial fibrillation.* The pharmacology of diltiazem is discussed in detail in Chapter 19.

MISCELLANEOUS ANTIARRHYTHMIC AGENTS

Digitalis Glycosides and Vagomimetic Drugs

Digitalis glycosides, especially digoxin (*Lanoxin*), because of their positive inotropic effects, are widely used for treating patients with congestive heart failure. They also continue to be used for the management of patients with supraventricular arrhythmias. Since the digitalis glycosides are discussed elsewhere (see Chapter 15), a full discussion of their mechanism of action is not provided here.

Digitalis glycosides enhance the inotropic state by increasing the intracellular calcium concentration. Intracellular calcium overload is also the mechanism for proarrhythmia associated with digitalis intoxication. The direct effect of digitalis on the electrophysiology of the myocytes is to increase the slope of phase 4 depolarization, an effect that enhances automaticity.

The principal antiarrhythmic effect is achieved via prominent vagotonic actions. The vagotonic influence leads to inhibition of Ca^{++} currents in the A-V node and activation of acetylcholine-sensitive potassium channels in the atrium (these channels are not present in the ventricle). This results in a slowing of conduction through the A-V node, a hyperpolarization of the resting membrane potential, and a shortening of the refractory period in atrial tissue. The principal antiarrhythmic actions are associated with the effects on the A-V node. Digitalis can therefore be used on reentrant arrhythmias that use the A-V node as one limb of the circuit and for limiting A-V conduction during rapid atrial arrhythmias, such as in atrial fibrillation.

Digitalis glycosides have theoretical advantages over other medications that limit conduction through the A-V-node, such as β-blockers and Ca^{++} channel blockers, by providing a positive rather than negative inotropic effect on the ventricles. The effects on the A-V node are limited, however, in states of heightened sympathetic tone, such as during advanced heart failure.

Adenosine

Adenosine (*Adenocard*) is an endogenous nucleoside that is a product of the metabolism of adenosine triphosphate. It is used for the rapid termination of supraventricular arrhythmias following rapid bolus dosing.

Electrophysiological Actions

Adenosine receptors are found on myocytes in the atria and sinoatrial and A-V nodes. Stimulation of these receptors acts via a G-protein signaling cascade to open an acetylcholine-sensitive outward potassium current. This leads to hyperpolarization of the resting membrane potential, a decrease in the slope of phase 4 spontaneous depolarization, and shortening of the action potential duration.

The effects on the A-V node may result in a conduction block and the termination of tachycardias that use the A-V node as a limb of a reentrant circuit. Adenosine does not affect the action potential of ventricular myocytes because the adenosine-stimulated potassium channel is absent in ventricular myocardium.

Electrocardiographic Changes

The most profound effect of adenosine is the induction of an A-V block within 10 to 20 seconds of administration. Mild sinus slowing may be observed initially followed by sinus tachycardia. There is no effect on the QRS duration or QT interval. Rarely, an adenosine bolus injection is accompanied by atrial fibrillation or ventricular tachyarrhythmias.

Hemodynamic Effects

The administration of a bolus dose of adenosine is associated with a biphasic pressor response. There is an initial brief increase in blood pressure followed by vasodilation and secondary tachycardia.

Pharmacokinetics

The pharmacokinetic characteristics of adenosine:

Oral bioavailability	Not measured
Onset of action	10 seconds (IV)
Peak response	Not measured
Duration of action	10–20 seconds
Plasma half-life	<10 seconds
Primary route of metabolism	Red blood cells
Primary route of excretion	Renal; inactive metabolites
Therapeutic serum concentration	Not applicable

Clinical Uses

Adenosine is approved for the acute management and termination of supraventricular tachyarrhythmias, in-

cluding A-V nodal reentrant tachycardia and A-V reciprocating tachycardia. Adenosine may be helpful in the diagnosis of atrial flutter.

Adverse Effects

Adverse reactions to the administration of adenosine are fairly common; however, the short half-life of the drug limits the duration of such events. The most common adverse effects are flushing, chest pain, and dyspnea. Adenosine may induce profound bronchospasm in patients with known reactive airway disease. The mechanism for bronchospasm is unclear, and the effect may last for up to 30 minutes despite the short half-life of the drug.

Contraindications

Patients with second- or third-degree A-V block should not receive adenosine. As indicated previously, the use of adenosine in asthmatic patients may exacerbate the asthmatic symptoms.

Drug Interactions

Metabolism of adenosine is slowed by dipyridamole, indicating that in patients stabilized on dipyridamole the therapeutically effective dose of adenosine may have to be increased. Methylxanthines antagonize the effects of adenosine via blockade of the adenosine receptors.

Magnesium Sulfate

Magnesium sulfate may be effective in terminating refractory ventricular tachyarrhythmias, particularly polymorphic ventricular tachycardia. Digitalis-induced arrhythmias are more likely in the presence of magnesium deficiency. Magnesium sulfate can be administered orally, intramuscularly, or, preferably, intravenously, when a rapid response is intended. The loss of deep tendon reflexes is a sign of overdose.

Drug–Device Interactions

The first implantable cardioverter–defibrillator (ICD) was placed in 1982. Since that time, their use has expanded exponentially. Several large clinical trials have demonstrated the superiority of ICDs compared with pharmacological therapy for the secondary prevention of arrhythmic death and possibly as primary therapy for patients at risk for ventricular arrhythmias.

Combination therapy employing both antiarrhythmic drugs and ICDs is becoming more common. While the antiarrhythmic drugs have multiple positive effects on the overall therapy, they may alter the frequency of ICD discharge and the ability of the device to detect ventricular tachycardia. A serious concern is the potential for a given drug to increase the defibrillation threshold, thereby rendering the device ineffective.

In general, drugs that block the sodium channel and shorten the action potential tend to increase the defibrillation threshold. Drugs that prolong repolarization also tend to decrease this threshold. These changes have obvious important ramifications for patients with ICDs.

Effects of antiarrhythmic drugs on defibrillation thresholds:

No change	Increase	Decrease
Quinidine	Amiodarone	Sotalol
Procainamide	Flecainide	Dofetilide
Disopyramide	Lidocaine	
Digitalis	Propafenone	
β-blockers	Mexiletine	

Study Questions

1. A 45-year-old woman has had recurrent episodes of atrial fibrillation. She is receiving phenytoin and quinidine to control the atrial fibrillation. She is also taking a low dose of diazepam for insomnia and estrogen replacement therapy. You learn today that she has been receiving ciprofloxacin for a urinary track infection. The reason for her appointment today is that she has been having ringing in the ears, headache, nausea, and blurred vision. She tells you that she is also having trouble hearing the television. You suspect drug toxicity. The most likely agent is
(A) Ciprofloxacin
(B) Estrogen
(C) Phenytoin
(D) Diazepam
(E) Quinidine

2. You are asked to treat a 55-year-old patient for continuing ventricular arrhythmias. The patient is receiving timolol drops for glaucoma, daily insulin injections for diabetes mellitus, and an ACE inhibitor for hypertension. You decide to use phenytoin instead of procainamide because of what pharmacological effect of procainamide?
(A) The local anesthetic effect of procainamide would potentiate diabetes.
(B) The anticholinergic effect of procainamide would aggravate glaucoma.

(C) The hypertensive effects of procainamide would aggravate the hypertension.
(D) The local anesthetic effect of procainamide would aggravate the hypertension.
(E) The cholinergic effects of procainamide would aggravate the diabetes.

3. Exercise-induced ventricular tachycardia in persons without overt cardiac disease is an example of delayed after-depolarizations and is characterized by an increase in intracellular ionized calcium. This type of arrhythmia is known to often respond well to which of the following combinations?
(A) β-Blocker and ACE inhibitor
(B) Calcium channel antagonist and ACE inhibitor
(C) α-Blocker and ACE inhibitor
(D) β-Blocker and calcium channel antagonist
(E) α-Blocker and calcium channel antagonist

4. Antiarrhythmic drugs are classified in four main groups based on their predominant mechanism of action. Antiarrhythmic agents in which class suppress abnormal automaticity and permit the sinoatrial node to again assume the role of the dominant pacemaker?
(A) Class I
(B) Class II
(C) Class III
(D) Class IV

5. Although most antiarrhythmic drugs (and indeed most drugs) are chemically synthesized, some compounds that occur endogenously in humans are useful. Indicate which of the following agents occurs endogenously and is a useful antiarrhythmic agent.
(A) Phenytoin
(B) Digoxin
(C) Adenosine
(D) Quinine
(E) Lidocaine

ANSWERS

1. **E.** Quinidine. These are the classic signs of cinchonism and are adverse effects of quinidine and quinine, constituents of the cinchona tree. Some of these effects could be seen as toxic effects of phenytoin. However, auditory acuity is associated with cinchonism and not with phenytoin toxicity. Nausea but not the other effects could be associated with ciprofloxacin. Excessive drowsiness would be expected if diazepam were involved. These effects would not be expected with the estrogen replacement therapy.
2. **B.** Anticholinergic agents, such as procainamide and disopyramide, are relatively contraindicated in patients with glaucoma. Procainamide is hypotensive rather than hypertensive. The local anesthetic activity of procainamide would have no adverse interaction with the diabetes mellitus.
3. **B.** Each of these approaches would reduce the tissue calcium concentration and prevent arrhythmias. Agents with α-blocking capacity would have no effect on calcium. Agents with ACE inhibitory activity would likewise have no effect on calcium.
4. **A.** Class I agents suppress both normal Purkinje fiber and His bundle automaticity in addition to abnormal automaticity resulting from myocardial damage. Class II drugs block β-adrenoceptors; class III drugs prolong the membrane action potential by delaying repolarization; and class IV drugs block the slow inward movement of calcium ions.
5. **C.** Adenosine is a product of the metabolism of adenosine triphosphate. Phenytoin and lidocaine are totally synthetic, while digoxin occurs naturally in plants and quinine occurs in the cinchona tree.

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A previously healthy 14-year-old athletic girl complained to her physician of a 6-day history of cough, with 2 days of fever, headache, and mild dyspnea. Several of her schoolmates had similar symptoms and were treated with antibiotics. Her physical examination revealed soft crackles at the bases of her lungs bilaterally. A chest radiograph demonstrated mild interstitial haziness at the bases. A diagnosis of community-acquired pneumonia was made, and she was given a prescription for 10 days of erythromycin. On the second day of therapy while at home, she suddenly lost consciousness while preparing breakfast and developed convulsive seizures on the floor. The emergency medical team was called and found her unresponsive. No pulse was detectable and the initial heart rhythm is shown below. Cardiopulmonary resuscitation was initiated and then DC cardioversion was performed with a return to sinus rhythm. Lidocaine was administered and she was transported to the local hospital. Her presenting ECG is shown below. What is her diagnosis?

ANSWER: Long QT syndrome. LQTS is caused by an abnormality in the function of specific ion channels responsible for myocardial repolarization. This may result from congenital mutations in the DNA encoding the ion channels (inherited form) or may be acquired from pharmacological therapy or other illness (increased intracerebral pressure, for example). In this patient's case, an abnormally long heart rate corrected QT interval was present on her ECG, diagnostic of a cardiac repolarization abnormality. After stopping the erythromycin, she was found to have an underlying long QT interval that was exacerbated by the erythromycin. A detailed family history confirmed the diagnosis when it was revealed that her mother had fainted on several occasions, and her first cousin (maternal) drowned while swimming in a lake 3 summers previously. Her physicians began β-blocker therapy and recommended placing an implantable cardioverter–defibrillator. Several medications prolong cardiac repolarization. The alteration in repolarization normally results from blockade of the rapid component of the delayed rectifier potassium current. In susceptible patients, this may lead to a profound prolongation of the QT interval and place them at risk for developing polymorphic ventricular tachycardia (torsades de pointe), which may degenerate into ventricular fibrillation and death. In this patient's case, a thorough investigation of all her relatives should be performed to search for family members with abnormal ECGs. In addition to the β-blocker and ICD therapy that was instituted, the patient was given a list of drugs to avoid because of their known QT-prolonging effects. A resource for patients with LQTS including a comprehensive list of QT interval prolonging drugs can be found on the internet at www.SADS.org.