Chapter 30

Antiarrhythmic Drugs

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Cardiac cells undergo depolarization and repolarization about 60 times per minute to form and propagate cardiac action potentials. The shape and duration of each action potential are determined by the activity of ion channel protein complexes in the membranes of individual cells, and the genes encoding most of these proteins and their regulators now have been identified. Action potentials in turn provide the primary signals to release Ca^{2+} from intracellular stores and to thereby initiate contraction. Thus, each normal heartbeat results from the highly integrated electrophysiological behavior of multiple proteins on the surface and within multiple cardiac cells. Disordered cardiac rhythm can arise from influences such as inherited variation in ion channel or other genes, ischemia, sympathetic stimulation, or myocardial scarring. Available antiarrhythmic drugs suppress arrhythmias by blocking flow through specific ion channels or by altering autonomic function. An increasingly sophisticated understanding of the molecular basis of normal and abnormal cardiac rhythm may lead to identification of new targets for antiarrhythmic drugs and perhaps improved therapies (Dobrev et al., 2012; Van Wagoner et al., 2015).

Arrhythmias can range from incidental, asymptomatic clinical findings to life-threatening abnormalities. Mechanisms underlying cardiac arrhythmias have been identified in cellular and animal experiments. For some human arrhythmias, precise mechanisms are known, and treatment can be targeted specifically to those mechanisms. In other cases, mechanisms can be only inferred, and the choice of drugs is based largely on results of prior experience. Antiarrhythmic drug therapy has two goals: termination of an ongoing arrhythmia or prevention of an arrhythmia. Unfortunately, antiarrhythmic drugs may not only help control arrhythmias but also can cause them, even during long-term therapy. Thus, prescribing antiarrhythmic drugs requires that precipitating factors be excluded or minimized, that a precise diagnosis of the type of arrhythmia (and its possible mechanisms) be made, that the prescriber has reason to believe that drug therapy will be beneficial, and that the risks of drug therapy can be minimized.

Principles of Cardiac Electrophysiology

The flow of ions across cell membranes generates the currents that make up cardiac action potentials. Factors that determine the magnitude of individual currents and their modulation by drugs include transmembrane potential, time since depolarization, or the presence of specific ligands (Nerbonne and Kass, 2005; Priori et al., 1999). Further, because the function of many channels is time and voltage dependent, even a drug that targets a single ion channel may, by altering the trajectory of the action potential, alter the function of other channels. Most antiarrhythmic drugs affect more than one ion current, and many exert ancillary effects, such as modification of cardiac contractility or autonomic nervous system function. Thus, antiarrhythmic drugs usually exert multiple actions and can be beneficial or harmful in individual patients (Priori et al., 1999; Roden, 1994).

The Cardiac Cell at Rest: a K^+-Permeable Membrane

Ions move across cell membranes in response to electrical and concentration gradients, not through the lipid bilayer but through specific ion channels or transporters. The normal cardiac cell at rest maintains a transmembrane potential approximately 80 to 90 mV negative to the exterior; this gradient is established by pumps, especially the Na^+, K^+–ATPase, and fixed anionic charges within cells. There are both an electrical and a

Abbreviations

AF: atrial fibrillation/flutter
4-AP: 4-aminopyridine
AV: atrioventricular
β blocker: β adrenergic receptor antagonist
CPVT: catecholaminergic polymorphic ventricular tachycardia
DAD: delayed afterdepolarization
DC: direct current
EAD: early afterdepolarization
ECG: electrocardiogram
ERP: effective refractory period
GX: glycine xylidide
HERG: *human ether-a-go-go related gene*
ICD: implantable cardioverter-defibrillator
IV: intravenous
LQTS: long QT syndrome
LV: left ventricle
NCX: Na^+-Ca^{2+} exchanger
PSVT: paroxysmal supraventricular tachycardia
RV: right ventricle
RyR2: ryanodine receptor type 2
SA: sinoatrial
SERCA2: SR-Ca^{2+} ATPase
SR: sarcoplasmic reticulum
VF: ventricular fibrillation
VT: ventricular tachycardia
WPW: Wolff-Parkinson-White

concentration gradient that would move Na^+ ions into resting cells (Figure 30–1). However, Na^+ channels, which allow Na^+ to move along this gradient, are closed in the cardiac cell at rest, so Na^+ does not enter normal resting cardiac cells. In contrast, a specific type of K^+ channel protein (the inward rectifier channel) remains open at negative resting potentials. Hence, K^+ can move through these channels across the cell membrane at negative potentials in response to either electrical or concentration gradients (Figure 30–1). For each individual ion, there is an equilibrium potential E_x at which there is no net driving force for the ion to move across the membrane. E_x can be calculated using the Nernst equation:

$$E_x = -(RT/FZx)\ln([x]_i/[x]_o) \qquad (30–1)$$

where Zx is the valence of the ion, T is the absolute temperature, R is the gas constant, F is Faraday's constant, $[x]_o$ is the extracellular concentration of the ion, and $[x]_i$ is the intracellular concentration. For typical values for K^+, $[K]_o$ = 4 mM and $[K]_i$ = 150 mM, the calculated K^+ equilibrium potential E_K is –96 mV. There is thus no net force driving K^+ ions into or out of a cell when the transmembrane potential is –96 mV, which is close to the resting potential. If $[K]_o$ is elevated to 10 mM, as might occur in diseases such as renal failure or myocardial ischemia, the calculated E_K rises to –70 mV. In this situation, there is excellent agreement between changes in theoretical E_K owing to changes in $[K]_o$ and the actual measured transmembrane potential, indicating that the normal cardiac cell at rest is permeable to K^+ (because inward rectifier channels are open) and that $[K]_o$ is the major determinant of resting potential.

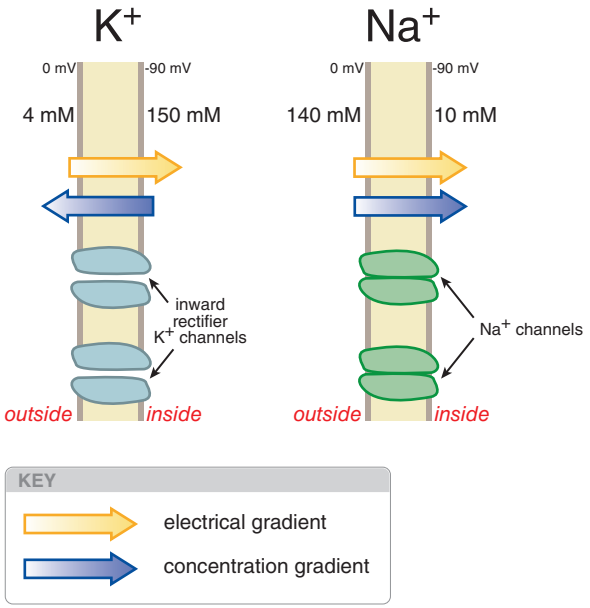


Figure 30–1 *Electrical and chemical gradients for K^+ and for Na^+ in a resting cardiac cell.* Inward rectifier K^+ channels are open (left), allowing K^+ ions to move across the membrane and the transmembrane potential to approach E_K. In contrast, Na^+ does not enter the cell despite a large net driving force because Na^+ channel proteins are in the closed conformation (right) in resting cells.

The Cardiac Action Potential

Transmembrane current through voltage-gated ion channels is the primary determinant of cardiac action potential morphology and duration. Channels are macromolecular complexes consisting of a pore-forming transmembrane structure (which may be a single protein, often termed an α subunit, or a multimer), as well as function-modifying β subunits and other accessory proteins. Common features of the pore-forming structure include a voltage-sensing domain, a selectivity filter, a conducting pore, and an inactivating particle (Figure 30–2; see also Figure 22–2). In response to changes in local transmembrane potential, ion channels undergo conformational changes, allowing for, or preventing, the flow of ions through the conducting pore along their electrochemical gradient, generally in time-, voltage-, or ligand-dependent fashion.

To initiate an action potential, a cardiac myocyte at rest is depolarized above a threshold potential, usually via gap junctions by a neighboring myocyte. On membrane depolarization, Na^+ channel proteins change conformation from the "closed" (resting) state to the "open" (conducting) state (Figure 30–2), allowing up to 10^7 Na^+ ions/s to enter each cell and moving the transmembrane potential toward E_{Na} (+65 mV). This surge of Na^+ ions lasts only about a millisecond, after which the Na^+ channel protein rapidly changes conformation from the open state to an "inactivated," nonconducting state (Figure 30–2). The maximum upstroke slope of phase 0 (dV/dt_{max}, or V_{max}) of the action potential (Figure 30–3) is largely governed by

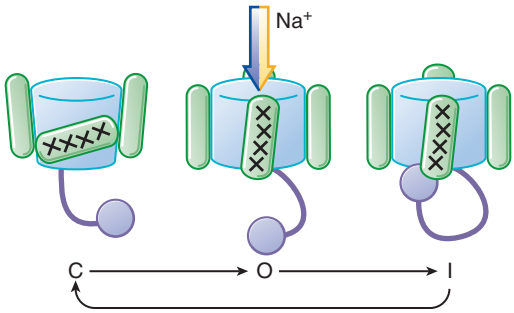


Figure 30–2 *Voltage-dependent conformational changes determine current flow through Na^+ channels.* At hyperpolarized potentials, the channel is in a closed conformation, and no current can flow (left). As depolarization begins, the voltage sensor (indicated here as ++++) moves, thus altering channel conformation and opening the pore, allowing conduction (middle). As depolarization is maintained, an intracellular particle blocks current flow, making the channel nonconducting in this inactivated state (right).

Na^+ current and is a major determinant of conduction velocity of a propagating action potential. Under normal conditions, Na^+ channels, once inactivated, cannot reopen until they reassume the closed conformation. However, a small population of Na^+ channels may continue to open during the action potential plateau in some cells (Figure 30–3), providing further inward current, often termed a "late" Na^+ current. As the cell membrane repolarizes, the negative membrane potential moves Na^+ channel proteins from inactivated to closed conformations, from which they are again available to open and depolarize the cell. The relationship between Na^+ channel availability and transmembrane potential is an important determinant of conduction and refractoriness in many cells, as discussed in the material that follows.

The changes in transmembrane potential generated by the inward Na^+ current produce, in turn, a series of openings (and in some cases subsequent inactivation) of other channels (Figure 30–3). For example, when a cell is depolarized by the Na^+ current, "transient outward" K^+ channels quickly change conformation to enter an open, or conducting, state; because the transmembrane potential at the end of phase 0 is positive to E_K, the opening of transient outward channels results in an outward, or repolarizing, K^+ current (termed I_{TO}), which contributes to the phase 1 "notch" seen in some action potentials (e.g., more prominent in epicardium than in endocardium). Transient outward K^+ channels, like Na^+ channels, inactivate rapidly. During the phase 2 plateau of a normal cardiac action potential, inward, depolarizing currents, primarily through L-type Ca^{2+} channels, are balanced by outward, repolarizing currents primarily through K^+ ("delayed rectifier") channels. Delayed rectifier currents (collectively termed I_K) increase with time, whereas Ca^{2+} currents inactivate (and so decrease with time); as a result, cardiac cells repolarize (phase 3) several hundred milliseconds after the initial Na^+ channel opening.

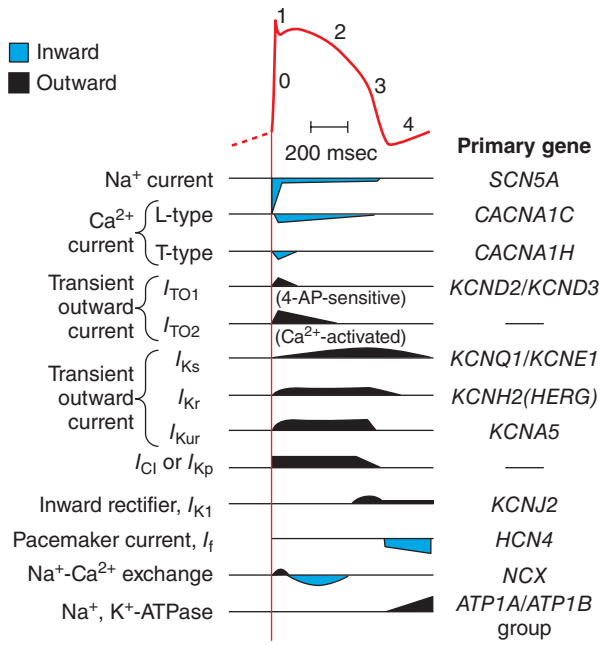


Figure 30–3 *The relationship between an action potential from the conducting system and the time course of the currents that generate it.* The current magnitudes are not to scale; the Na^+ current is ordinarily 50 times larger than any other current, although the portion that persists into the plateau (phase 2) is small. Multiple types of Ca^{2+} current, transient outward current I_{TO}, and delayed rectifier I_K have been identified. Each represents a different channel protein, usually associated with ancillary (function-modifying) subunits. 4-AP is a widely used in vitro blocker of K^+ channels. I_{TO2} may be a Cl^- current in some species. Components of I_K have been separated on the basis of how rapidly they activate: slowly (I_{Ks}), rapidly (I_{Kr}), or ultrarapidly (I_{Kur}). The voltage-activated, time-independent current may be carried by Cl^- (I_{Cl}) or K^+ (I_{Kp}, *p* for plateau). The genes encoding the major pore-forming proteins have been cloned for most of the channels shown here and are listed in the right-hand column.

A common mechanism whereby drugs prolong cardiac action potentials and provoke arrhythmias is inhibition of a specific delayed rectifier current, I_{Kr}, generated by expression of *KCNH2* (formerly termed the *HERG*). The ion channel protein generated by *KCNH2* expression differs from other ion channels in important structural features that make it much more susceptible to drug block; understanding these structural constraints is an important first step to designing drugs lacking I_{Kr}-blocking properties (Mitcheson et al., 2000). Avoiding I_{Kr}/*KCNH2* channel block has become a major issue in drug development (Roden, 2004).

Maintenance of Intracellular Ion Homeostasis

With each action potential, the cell interior gains Na^+ ions and loses K^+ ions. An ATP-requiring Na^+-K^+ exchange mechanism, or pump, is activated in most cells to maintain intracellular homeostasis. This Na^+, K^+–ATPase extrudes three Na^+ ions for every two K^+ ions shuttled from the exterior of the cell to the interior; as a result, the act of pumping itself is electrogenic, generating a net outward (repolarizing) current.

Normally, intracellular Ca^{2+} is maintained at very low levels (<100 nM). In cardiac myocytes, the entry of Ca^{2+} during each action potential through L-type Ca^{2+} channels is a signal to the SR to release its Ca^{2+} stores, and thus initiate Ca^{2+}-dependent contraction, a process termed excitation-contraction coupling. The efflux of Ca^{2+} from the SR occurs through ryanodine receptor release channels (RyR2) and subsequent removal of intracellular Ca^{2+} occurs by both SERCA2, which moves Ca^{2+} ions back into the SR, and an electrogenic NCX on the cell surface, which exchanges three Na^+ ions from the exterior for each Ca^{2+} ion extruded.

Genetic Arrhythmia Diseases

Rare congenital arrhythmia diseases such as the LQTS and CPVT can cause sudden death due to fatal arrhythmias, often in young subjects. The identification of disease genes not only has resulted in improved care of affected patients and their families but also has contributed importantly to our understanding of the normal action potential, arrhythmia mechanisms, and potential antiarrhythmic drug targets (Keating and Sanguinetti, 2001). For example, mutations in the cardiac Na^+ channel gene *SCN5A* can cause one form of LQTS by destabilizing fast inactivation, increasing late Na^+ current, thereby prolonging action potentials, and thus the QT interval (as discussed in material that follows). Drugs inhibiting this abnormal current may be antiarrhythmic in this form of LQTS (Remme and Wilde, 2013), and drugs increasing late Na^+ current may cause arrhythmias (Yang et al., 2014). Inhibitors may include not only antiarrhythmics such as mexiletine or flecainide discussed in this chapter, but also the antianginal agent ranolazine (see Chapter 28), which appears to be a late Na^+ current blocker.

Similarly, mutations in the *RyR2* gene encoding an intracellular Ca^{2+} release channel (or less commonly in other genes regulating RyR2 function) cause CPVT by generating "leaky" RyR2 channels, perturbing intracellular Ca^{2+} homeostasis and causing DAD-dependent arrhythmias described further in this chapter. Drugs such as flecainide and propafenone that inhibit these abnormal RyR2 channels appear to prevent CPVT in mouse models and in humans (Watanabe et al., 2009). Intriguingly, some arrhythmias in acquired heart disease have been attributed to increased late Na^+ current or leaky RyR2 channels. Thus, studies in the rare congenital arrhythmia syndromes may point to new avenues for drug development in more common arrhythmias in acquired heart disease (Knollmann and Roden, 2008 Priori et al., 1999).

Action Potential Heterogeneity in the Heart

The general description of the action potential and the currents that underlie it must be modified for certain cell types (Figure 30–4), primarily due to variability in the expression of ion channels and electrogenic ion transport pumps. The resultant diversity of action potentials in different regions of the heart plays a role in understanding the pharmacological profiles of antiarrhythmic drugs. In the ventricle, action potential duration varies across the wall of each chamber, as well as apicobasally, largely as a consequence of varying densities of repolarizing currents. In the

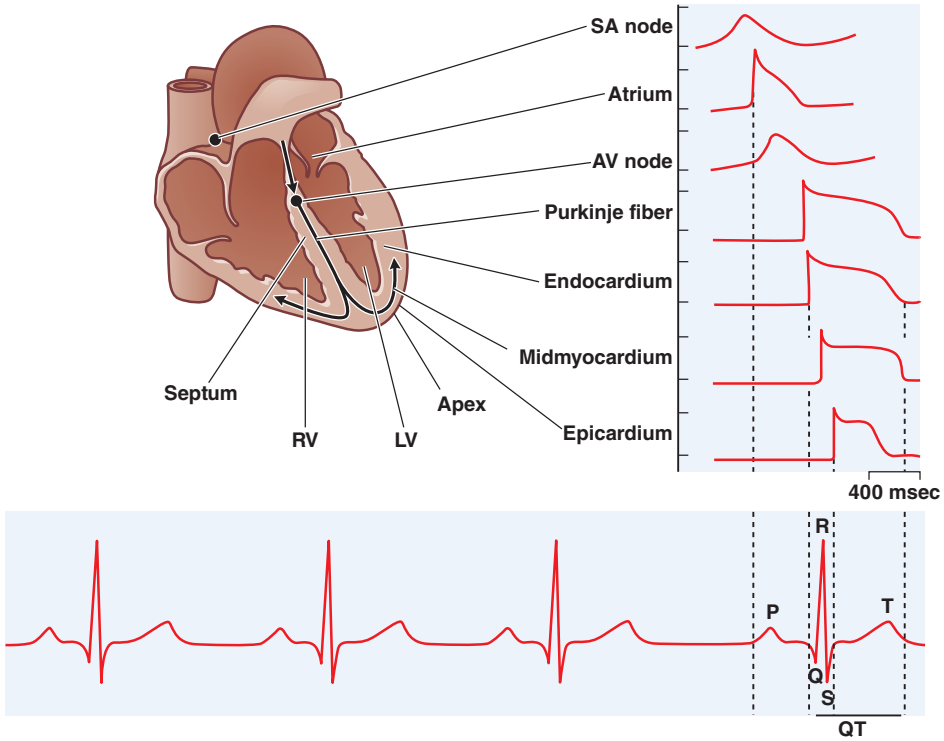


Figure 30–4 *Normal impulse propagation*. A schematic of the human heart with example action potentials from different regions of the heart (top) for a normal beat and their corresponding contributions to the macroscopic ECG (bottom). (Reproduced with permission from Nerbonne JM, Kass RS. Molecular physiology of cardiac repolarization. *Physiol Rev*, **2005**, 85:1205–1253. Used with permission of the American Physiological Society.)

neighboring His-Purkinje conduction system, action potentials are longer, probably due to decreased K^+ currents, increased "late" Na^+ currents, and differences in intercellular Ca^{2+} handling (Dun and Boyden, 2008).

Atrial cells have shorter action potentials than ventricular cells because of larger early repolarization currents such as I_{TO}. Atrial cells also express an additional repolarizing K^+ channel that is activated by the neurotransmitter acetylcholine and accounts for action potential shortening with vagal stimulation. Cells of the sinus and AV nodes lack substantial Na^+ currents, and depolarization is achieved by inward current generated by opening of Ca^{2+} channels. In addition, these cells, as well as cells from the conducting system, normally display the phenomenon of spontaneous diastolic, or phase 4, depolarization and thus spontaneously reach threshold for regeneration of action potentials. The rate of spontaneous firing usually is fastest in sinus node cells, which therefore serve as the natural pacemaker of the heart. The slow diastolic depolarization that underlies pacemaker activity is generated by a nonselective channel that conducts both Na^+ and K^+ and is activated at hyperpolarized membrane potentials (Cohen and Robinson, 2006). In diseased cells, pacemaker-like activity can arise from spontaneous Ca^{2+} release from the SR, followed by membrane depolarization due to activation of NCX.

Certain ion channels are expressed only in some tissues or become active only under specific pathophysiologic conditions. For example, the T-type Ca^{2+} channel may be important in diseases such as hypertension and play a role in pacemaker activity (Ono and Iijima, 2010). A T-type-selective Ca^{2+} channel antagonist, *mibefradil* was commercially available briefly in the late 1990s but was withdrawn because of concerns over potentially life-threatening pharmacokinetic interactions with many other drugs. A second example is a channel that transports Cl^- ions and results in repolarizing currents (I_{Cl}) (Duan, 2013); some of these are observed only in association with pathophysiological conditions. A third example is the K^+ channel that are quiescent when intracellular ATP stores are normal and become active when these stores are depleted. Such ATP-inhibited K^+ channel may become particularly important in repolarizing cells during states of metabolic stress such as myocardial ischemia (Tamargo et al., 2004).

Impulse Propagation and the Electrocardiogram

Normal cardiac impulses originate in the sinus node. Impulse propagation in the heart depends on the magnitude of the depolarizing current (usually Na^+ current) and the geometry and density of cell-cell electrical connections (Kleber and Saffitz, 2014). Cardiac cells are relatively long and thin and well coupled through specialized gap junction proteins at their ends, whereas lateral ("transverse") gap junctions are sparser. As a result, impulses spread along cells two to three times faster than across cells. This "anisotropic" (direction-dependent) conduction may be a factor in the genesis of certain arrhythmias described in the material that follows (Priori et al., 1999).

Once impulses leave the sinus node, they propagate rapidly throughout the atria, resulting in atrial systole and the P wave of the surface ECG (Figure 30–4). Propagation slows markedly through the AV node, where the inward current (through Ca^{2+} channels) is much smaller than the Na^+ current in atria, ventricles, or the subendocardial conducting system. This conduction delay, represented as the PR interval on the ECG, allows the atrial contraction to propel blood into the ventricle, thereby optimizing cardiac output.

Once impulses exit the AV node, they enter the conducting system, where Na^+ currents are larger than in any other tissue, and propagation is correspondingly faster, up to 0.75 m/s longitudinally. Activation spreads from the His-Purkinje system on the endocardium of the ventricles throughout the rest of the ventricles, stimulating coordinated ventricular contraction. This electrical activation manifests itself as the QRS complex on the ECG. Ventricular repolarization is presented on the surface ECG as the T wave. The time from initial depolarization in the ventricle until the end of repolarization is termed the QT interval. Lengthening of ventricular action potentials prolongs the QT interval and may be associated with arrhythmias in LQTS and other settings.

Refractoriness and Conduction Failure

In atrial, ventricular, and His-Purkinje cells, if a restimulation occurs very early during the plateau of an action potential, no Na^+ channels are

available to open, so no inward current results, and no new action potential is generated: At this point, the cell is termed *refractory* (Figure 30–5). On the other hand, if a stimulus occurs after the cell has repolarized completely, Na^+ channels have recovered from inactivation, and a normal Na^+ channel–dependent upstroke results with the same amplitude as the previous upstroke (Figure 30–5A). When a stimulus occurs during phase 3 of the action potential, the upstroke of the premature action potential is slower and of smaller magnitude. The magnitude depends on the number of Na^+ channels that have recovered from inactivation (Figure 30–5A), which in turn is dependent on the membrane potential. Thus, refractoriness is determined by the voltage-dependent recovery of Na^+ channels from inactivation.

Refractoriness frequently is measured by assessing whether premature stimuli applied to tissue preparations (or the whole heart) result in propagated impulses. While the magnitude of the Na^+ current is one major determinant of propagation of premature beats, cellular geometry also is important in multicellular preparations. Propagation from cell to cell requires current flow from the first site of activation and consequently can fail if inward current is insufficient to drive activation in many neighboring cells. The *ERP* is the longest interval at which a premature stimulus fails to generate a propagated response and often is used to describe drug effects in intact tissue.

The situation is different in tissue whose depolarization is largely controlled by Ca^{2+} channel current, such as the AV node. Because Ca^{2+} channels have a slower recovery from inactivation, these tissues are often referred to as *slow response* (Figure 30–5C), in contrast to *fast response* in the remaining cardiac tissues. Even after a Ca^{2+} channel–dependent action potential has repolarized to its initial resting potential, not all Ca^{2+} channels are available for reexcitation. Therefore, an extra stimulus applied shortly after repolarization is complete generates a reduced Ca^{2+} current, which may propagate slowly to adjacent cells prior to extinction. An extra stimulus applied later will result in a larger Ca^{2+} current

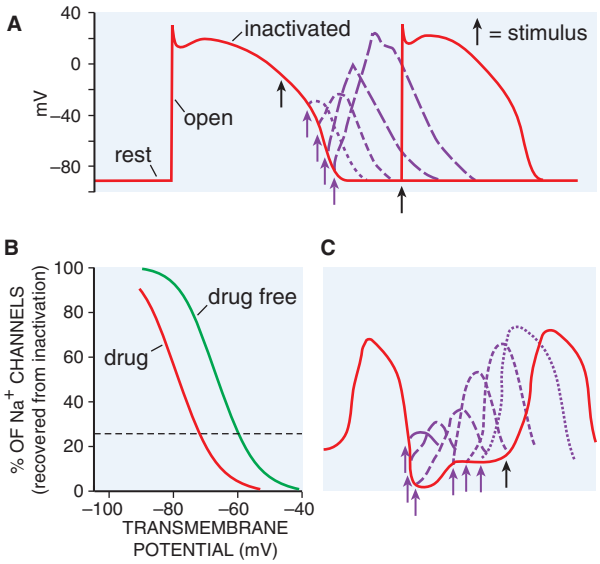


Figure 30–5 *Qualitative differences in responses of nodal and conducting tissues to premature stimuli.* **A.** With a very early premature stimulus (black arrow) in ventricular myocardium, all Na^+ channels still are in the inactivated state, and no upstroke results. As the action potential repolarizes, Na^+ channels recover from the inactivated to the resting state, from which opening can occur. The phase 0 upstroke slopes of the premature action potentials (purple) are greater with later stimuli because recovery from inactivation is voltage-dependent. **B.** The relationship between transmembrane potential and degree of recovery of Na^+ channels from inactivation. The dotted line indicates 25% recovery. Most Na^+ channel–blocking drugs shift this relationship to the left. **C.** In Ca^{2+}-dependent slow-response tissues such as the AV node, premature stimuli delivered even after full repolarization of the action potential are depressed; recovery from inactivation is time-dependent.

and faster propagation. Thus, in Ca^{2+} channel–dependent tissues, which include not only the AV node but also tissues whose underlying characteristics have been altered by factors such as myocardial ischemia, refractoriness is prolonged, and propagation occurs slowly. Conduction that exhibits such dependence on the timing of premature stimuli is termed *decremental*. Slow conduction in the heart, a critical factor in the genesis of reentrant arrhythmias (see further discussion), also can occur when Na^+ currents are depressed by disease or membrane depolarization (e.g., elevated $[K]_o$), resulting in decreased steady-state Na^+ channel availability (Figure 30–5B).

Mechanisms of Cardiac Arrhythmias

An arrhythmia is by definition a perturbation of the normal sequence of impulse initiation and propagation. Failure of impulse initiation, in the sinus node, may result in slow heart rates (bradyarrhythmias), whereas failure in the normal propagation of action potentials from atrium to ventricle results in dropped beats (commonly referred to as heart block) and usually reflects an abnormality in either the AV node or the His-Purkinje system. These abnormalities may be caused by drugs (Table 30–1) or by structural heart disease; in the latter case, permanent cardiac pacing may be required.

Abnormally rapid heart rhythms (tachyarrhythmias) are common clinical problems that may be treated with antiarrhythmic drugs. Three major underlying mechanisms have been identified: enhanced automaticity, triggered automaticity, and reentry. These are often interrelated mechanisms as abnormal beats arising from one mechanism can elicit a second; for example, a triggered automatic beat can initiate reentry.

Enhanced Automaticity

Enhanced automaticity may occur in cells that normally display spontaneous diastolic depolarization—the sinus and AV nodes and the His-Purkinje system. β Adrenergic stimulation, hypokalemia, and mechanical stretch of cardiac muscle cells increase phase 4 slope and so accelerate pacemaker rate, whereas *acetylcholine* reduces pacemaker rate both by decreasing phase 4 slope and by hyperpolarization (making the maximum diastolic potential more negative). In addition, automatic behavior may occur in sites that ordinarily lack spontaneous pacemaker activity; for example, depolarization of ventricular cells (e.g., by ischemia) may produce "abnormal" automaticity. When impulses propagate from a region of enhanced normal or abnormal automaticity to excite the rest of the heart, more complex arrhythmias may result from the induction of reentry.

Afterdepolarizations and Triggered Automaticity

Under some pathophysiological conditions, a normal cardiac action potential may be interrupted or followed by an abnormal depolarization (Figure 30–6). If this abnormal depolarization reaches threshold, it may, in turn, give rise to secondary upstrokes that can propagate and create abnormal rhythms. These abnormal secondary upstrokes occur only after an initial normal, or "triggering," upstroke and thus are termed *triggered rhythms*.

Two major forms of triggered rhythms are recognized. In the first case, under conditions of intracellular or SR Ca^{2+} overload (e.g., myocardial ischemia, adrenergic stress, digitalis intoxication, or CPVT), a normal action potential may be followed by a *DAD* (Figure 30–6A); as discussed previously, enhanced NCX current is thought to be a common mechanism underlying DADs. If this afterdepolarization reaches threshold, a secondary triggered beat or beats may occur. DAD amplitude is increased in vitro by rapid pacing, and clinical arrhythmias thought to correspond to DAD-mediated triggered beats are more frequent when the underlying cardiac rate is rapid (Priori et al., 1999).

In the second type of triggered activity, the key abnormality is marked prolongation of the cardiac action potential. When this occurs, phase 3 repolarization may be interrupted by an EAD (Figure 30–6B). EAD-mediated triggering in vitro and clinical arrhythmias are most common when the

TABLE 30–1 ■ DRUG-INDUCED CARDIAC ARRHYTHMIAS

ARRHYTHMIA	DRUG	LIKELY MECHANISM	TREATMENT*	CLINICAL FEATURES
Sinus bradycardia, AV block	Digoxin	↑Vagal tone	Antidigoxin antibodies, temporary pacing	Atrial tachycardia may also be present
Sinus bradycardia, AV block	Verapamil, diltiazem	Ca^{2+} channel block	Ca^{2+}, temporary pacing	
Sinus bradycardia	β Blockers	Sympatholytic	Isoproterenol	
AV block	Clonidine Methyldopa		Temporary pacing	
Sinus tachycardia Any other tachycardia	β Blocker withdrawal	Upregulation of β receptors with chronic therapy; β blocker withdrawal →↑β effects	β Blockade	Hypertension, angina also possible
↑Ventricular rate in atrial flutter	Quinidine Flecainide Propafenone	Conduction slowing in atrium, with enhanced (quinidine) or unaltered AV conduction	AV nodal blockers	QRS complexes often widened at fast rates
↑Ventricular rate in atrial fibrillation in patients with WPW syndrome	Digoxin Verapamil	↓ Accessory pathway refractoriness	IV procainamide DC cardioversion	Ventricular rate can exceed 300 beats/min
Multifocal atrial tachycardia	Theophylline	↑Intracellular Ca^{2+} and DADs	Withdraw theophylline ?Verapamil	Often in advanced lung disease
Polymorphic VT with ↑QT interval (torsades de pointes)	Quinidine Sotalol Procainamide Disopyramide Dofetilide Ibutilide "Noncardioactive" drugs (see text) Amiodarone (rare)	EAD-related triggered activity	Cardiac pacing Isoproterenol Magnesium	Hypokalemia, bradycardia frequent Related to ↑ plasma concentrations, except for quinidine
Frequent or difficult to terminate VT ("incessant" VT)	Flecainide Propafenone Quinidine (rarer)	Conduction slowing in reentrant circuits	Na^+ bolus reported effective in some cases	Most often in patients with advanced myocardial scarring
Atrial tachycardia with AV block; ventricular bigeminy, others	Digoxin	DAD-related triggered activity (± ↑ vagal tone)	Antidigoxin antibodies	Coexistence of abnormal impulses with abnormal sinus or AV nodal function
Ventricular fibrillation	Inappropriate use of IV verapamil	Severe hypotension and/or myocardial ischemia	Cardiac resuscitation (DC cardioversion)	Misdiagnosis of VT as PSVT and inappropriate use of verapamil

*In each of these cases, recognition and withdrawal of the offending drug(s) are mandatory ↑, increase; ↓, decrease; ?, unclear.

underlying heart rate is slow, extracellular K^+ is low, and certain drugs that prolong action potential duration (antiarrhythmics and others) are present. EAD-related triggered upstrokes probably reflect inward current through Na^+ or Ca^{2+} channels. Due to their intrinsically longer action potential, EADs are induced more readily in Purkinje cells and in endocardial than in epicardial cells.

When cardiac repolarization is markedly prolonged, polymorphic ventricular tachycardia with a long QT interval, termed *torsades de pointes*, may occur. This arrhythmia is thought to be caused by EADs, which trigger functional reentry (discussed next) owing to heterogeneity of action potential durations across the ventricular wall (Priori et al., 1999). Congenital LQTS, a disease in which *torsades de pointes* causes syncope or death, is most often caused by mutations in the genes encoding the Na^+ channels (10%) or the channels underlying the repolarizing currents I_{Kr} and I_{Ks} (80-90%) (Nerbonne and Kass, 2005).

Reentry

Reentry occurs when a cardiac impulse travels in a path such as to return to its original site and reactivate the original site, thus perpetuating rapid reactivation independent of normal sinus node function. Key features enabling reentrant excitation are a pathway; heterogeneity of electrophysiologic properties, notably refractoriness, along the pathway; and slow conduction.

Anatomically Defined Reentry

The prototypical example of reentry is the WPW syndrome in which patients have an accessory connection between the atrium and ventricle (Figure 30–7). With each sinus node depolarization, impulses can excite the ventricle via the normal structures (AV node) or the accessory pathway, and this often results in an unusual and characteristic QRS complex in normal sinus rhythm. Importantly, the electrophysiological properties of the AV node and accessory pathways are different: Accessory pathways usually consist of nonnodal tissue with longer refractory periods and without decremental conduction. Thus, with a premature atrial beat (e.g., from abnormal automaticity), conduction may fail in the accessory pathway but continue, albeit slowly, in the AV node and then through the His-Purkinje system; there the propagating impulse may encounter the ventricular end of the accessory pathway when it is no longer refractory. The likelihood

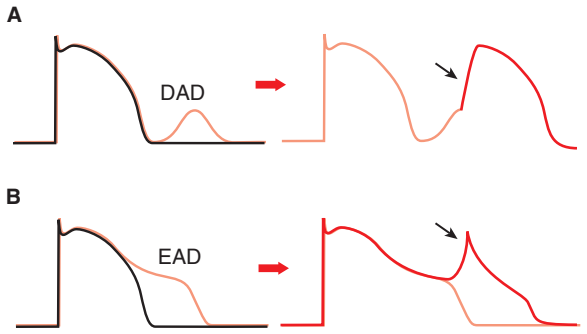


Figure 30–6 *Afterdepolarizations and triggered activity.* **A.** Delayed afterdepolarization arising after full repolarization. DADs are typically caused by spontaneous Ca^{2+} release from the SR under conditions of Ca^{2+} overload. The extracytosolic Ca^{2+} is removed from the cytosol by the electrogenic Na-Ca exchanger, which produces Na^+ influx and causes a cell membrane depolarization in the form of a DAD. A DAD that reaches threshold results in a triggered upstroke (black arrow, right). **B.** Early afterdepolarization interrupting phase 3 repolarization. Multiple ion channels and transporters can contribute to EADs (e.g., Na^+ channel, L-type Ca^{2+} channel, Na-Ca exchanger). Under some conditions, triggered beat(s) can arise from an EAD (black arrow, right).

that the accessory pathway is no longer refractory increases as AV nodal conduction slows, demonstrating how slow conduction enables reentry. When the impulse reenters the atrium, it then can reenter the ventricle via the AV node, reenter the atrium via the accessory pathway, and so on (Figure 30–7).

Reentry of this type, referred to as *AV reentrant tachycardia*, is determined by the following:

1. The presence of an anatomically defined circuit
2. Heterogeneity in refractoriness among regions in the circuit
3. Slow conduction in one part of the circuit

Similar "anatomically defined" reentry commonly occurs in the region of the AV node (*AV nodal reentrant tachycardia*), in the atrium (*atrial flutter*), and in scarred ventricle (*ventricular tachycardia*). The term *PSVT* includes both AV reentry and AV nodal reentry, which share many clinical features.

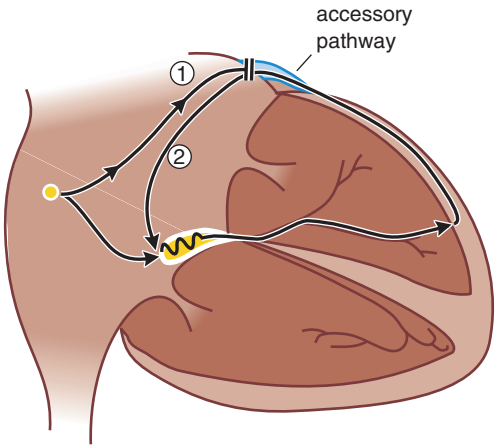


Figure 30–7 *Atrioventricular reentrant tachycardia in the WPW syndrome.* In these patients, an accessory AV connection is present (light blue). A premature atrial impulse blocks in the accessory pathway (1) and propagates slowly through the AV node and conducting system. On reaching the accessory pathway (by now no longer refractory), the impulse reenters the atrium (2), where it then can reenter the ventricle via the AV node and become self-sustaining (see Figure 30–9C). AV nodal blocking drugs readily terminate this tachycardia. Recurrences can be prevented by drugs that prevent atrial premature beats, by drugs that alter the electrophysiological characteristics of tissue in the circuit (e.g., they prolong AV nodal refractoriness), and by nonpharmacological ablation techniques that selectively destroy the accessory pathway.

While antiarrhythmic drugs or electrical cardioversion are used to terminate reentry acutely (discussed further in the chapter and Table 30–2), the primary therapy for anatomically defined reentry is radio-frequency ablation because its consistent pathway often makes it possible to identify and ablate critical segments of this pathway effectively, curing the patient and obviating the need for long-term drug therapy. Radio-frequency ablation is carried out through a catheter advanced to the interior of the heart and requires minimal convalescence.

Functionally Defined Reentry

Reentry also may occur in the absence of a distinct, anatomically defined pathway (Figure 30–8). For example, a premature beat from within the ventricular wall may encounter refractory tissue in only one direction, allowing for conduction throughout the rest of the wall until the originally refractory area recovers, reexcites, and then propagates back through the original location of the premature beat. Another example is localized ischemia or other electrophysiological perturbations that result in an area of sufficiently slow conduction in the ventricle that impulses exiting from that area find the rest of the myocardium reexcitable, in which case reentry may ensue. Atrial fibrillation and VF are extreme examples of "functionally defined" reentry: Cells are reexcited as soon as they are repolarized sufficiently to allow enough Na^+ channels to recover from inactivation. The abnormal activation pathway subsequently provides abnormal spatial heterogeneity of repolarization that can cause other reentrant circuits to form. In atrial fibrillation, these can persist for years, and rotor-like activity can sometimes be recorded, presumably reflecting reentrant circuits that can be transiently stable or meander around the atrium.

Common Arrhythmias and Their Mechanisms

The primary tool for diagnosis of arrhythmias is the ECG. More sophisticated approaches sometimes are used, such as recording from specific regions of the heart during artificial induction of arrhythmias by specialized pacing techniques. Table 30–2 lists common arrhythmias, their likely mechanisms, and approaches that should be considered for their acute termination and for long-term therapy to prevent recurrence. Examples of some arrhythmias discussed here are shown in Figure 30–9. Some arrhythmias, notably VF, are treated not pharmacologically but with DC cardioversion—the application of a large electric current across the chest. This technique also can be used to immediately restore normal rhythm in less-serious cases; if the patient is conscious, a brief period of general anesthesia is required. ICDs, devices that are capable of detecting VF and automatically delivering a defibrillating shock, are used increasingly in patients judged to be at high risk for VF. Often, drugs are used with these devices if defibrillating shocks, which are painful, occur frequently.

Mechanisms of Antiarrhythmic Drug Action

Antiarrhythmic drugs almost invariably have multiple effects in patients, and their effects on arrhythmias can be complex. A drug can modulate other targets in addition to its primary site of action. At the same time, a single arrhythmia may result from multiple underlying mechanisms (e.g., torsades de pointes [Figure 30–9H] can result either from increased Na^+ channel late currents or decreased inward rectifier currents). Thus, antiarrhythmic therapy should be tailored to target the most relevant underlying arrhythmia mechanism, where it is known. Drugs may be antiarrhythmic by suppressing the initiating mechanism or by altering reentrant circuits. In some cases, drugs may suppress an initiator but nonetheless promote reentry (see discussion that follows).

Drugs may slow automatic rhythms by altering any of the four determinants of spontaneous pacemaker discharge (Figure 30–10): (1) increase maximum diastolic potential, (2) decrease phase 4 slope, (3) increase threshold potential, or (4) increase action potential duration. *Adenosine* and acetylcholine may increase maximum diastolic potential, and β blockers (see Chapter 12) may decrease phase 4 slope. Blockade of Na^+ or Ca^{2+} channels usually results in altered threshold, and blockade of cardiac K^+ channels prolongs the action potential.

TABLE 30–2 ■ A MECHANISTIC APPROACH TO ANTIARRHYTHMIC THERAPY

ARRHYTHMIA	COMMON MECHANISM	ACUTE THERAPY[a]	CHRONIC THERAPY[a]
Premature atrial, nodal, or ventricular depolarizations	Unknown	None indicated	None indicated
Atrial fibrillation	Disorganized "functional" reentry Continual AV node stimulation and irregular, often rapid, ventricular rate	1. Control ventricular response: AV node block[b] 2. Restore sinus rhythm: DC cardioversion	1. Control ventricular response: AV nodal block[b] 2. Maintain normal rhythm: K^+ channel block, Na^+ channel block, Na^+ channel block with $\tau_{recovery}$ >1 sec
Atrial flutter	Stable reentrant circuit in the right atrium Ventricular rate often rapid and irregular	Same as atrial fibrillation Same as atrial fibrillation	Same as atrial fibrillation AV nodal blocking drugs especially desirable to avoid ↑ ventricular rate Ablation in selected cases[c]
Atrial tachycardia	Enhanced automaticity, DAD-related automaticity, or reentry in atrium	Adenosine sometimes effective Same as atrial fibrillation	Same as atrial fibrillation Ablation of tachycardia "focus"[c]
AV nodal reentrant tachycardia (PSVT)	Reentrant circuit within or near AV node	AV nodal block[b] Less commonly: ↑ vagal tone (digitalis, edrophonium, phenylephrine)	*AV nodal block Flecainide Propafenone *Ablation[c]
Arrhythmias associated with WPW syndrome: 1. AV reentry (PSVT)	Reentry (Figure 30–7)	Same as AV nodal reentry *DC cardioversion	K^+ channel block Na^+ channel block with $\tau_{recovery}$ >1 sec *Ablation[c]
2. Atrial fibrillation with atrioventricular conduction via accessory pathway	Very rapid rate due to nondecremental properties of accessory pathway	*Procainamide Lidocaine	K^+ channel block Na^+ channel block with $\tau_{recovery}$ >1 sec (AV nodal blockers can be harmful)
VT in patients with remote myocardial infarction	Reentry near the rim of the healed myocardial infarction	Amiodarone Procainamide DC cardioversion Adenosine[e]	*ICD[d] Amiodarone K^+ channel block Na^+ channel block
VT in patients without structural heart disease	DADs triggered by ↑ sympathetic tone	Verapamil[e] β Blockers[e] *DC cardioversion	Verapamil[e] β Blockers[e]
VF	Disorganized reentry	Lidocaine Amiodarone Procainamide Pacing	*ICD[d] Amiodarone K^+ channel block Na^+ channel block
Torsades de pointes, congenital or acquired; (often drug related)	EAD-related triggered activity	Magnesium Isoproterenol	β Blockade Pacing

*Indicates treatment of choice. [a]Acute drug therapy is administered intravenously; chronic therapy implies long-term oral use. [b]AV nodal block can be achieved clinically by adenosine, Ca^{2+} channel block, β adrenergic receptor blockade, or increased vagal tone (a major antiarrhythmic effect of digitalis glycosides). [c]Ablation is a procedure in which tissue responsible for the maintenance of a tachycardia is identified by specialized recording techniques and then selectively destroyed, usually by high-frequency radio waves delivered through a catheter placed in the heart. [d]ICD, implanted cardioverter–defibrillator: a device that can sense VT or VF and deliver pacing and/or cardioverting shocks to restore normal rhythm. [e]These may be harmful in reentrant VT and so should be used for acute therapy only if the diagnosis is secure.

Antiarrhythmic drugs may suppress arrhythmias owing to DADs or EADs by two major mechanisms:

1. inhibition of the development of afterdepolarizations; and
2. interference with the inward current (usually through Na^+ or Ca^{2+} channels), which is responsible for the upstroke

Thus, arrhythmias owing to DADs (i.e., due to *digitalis* toxicity or CPVT) may be inhibited by *verapamil* (which blocks the development of DAD by reducing Ca^{2+} influx into the cell, thereby decreasing SR Ca^{2+} load and the likelihood of spontaneous Ca^{2+} release from the SR) or by Na^+ channel–blocking drugs, which elevate the threshold required to produce the abnormal upstroke. In CPVT, more effective than *verapamil* is combined RyR2 and Na^+ channel block by agents such as *flecainide* or *propafenone*. Similarly, two approaches are used in arrhythmias related to EAD-triggered beats (Tables 30–1 and 30–2). EADs can be inhibited by shortening action potential duration; in practice, heart rate is accelerated by *isoproterenol* infusion or by pacing. Triggered beats arising from EADs can be inhibited by Mg^{2+} without normalizing repolarization in vitro or QT interval through mechanisms that are not well understood. In most forms of congenital LQTS, torsades de pointes occurs with adrenergic stress; therapy includes β adrenergic blockade (which does not shorten the QT interval but may prevent EADs) as well as pacing to shorten action potentials.

In anatomically determined reentry, drugs may terminate the arrhythmia by blocking propagation of the action potential. Conduction usually fails in a "weak link" in the circuit. In the example of the WPW-related arrhythmia described previously, the weak link is the AV node, and drugs that prolong AV nodal refractoriness and slow AV nodal conduction, such as Ca^{2+} channel blockers, β blockers, or adenosine, are likely to be effective. On the other hand, slowing conduction in functionally determined reentrant circuits may change the pathway without extinguishing the circuit. In fact, slow conduction generally promotes the development of reentrant

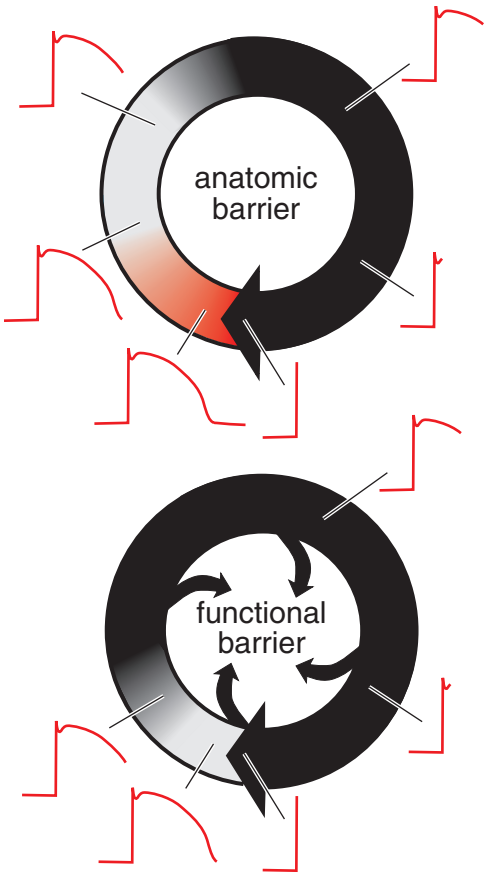


Figure 30–8 *Two types of reentry.* The border of a propagating wavefront is denoted by a heavy black arrowhead. In anatomically defined reentry (top), a fixed pathway is present (e.g., Figure 30–7). The black area denotes tissue in the reentrant circuit that is completely refractory because of the recent passage of the propagating wavefront; the gray area denotes tissue in which depressed upstrokes can be elicited (see Figure 30–5A), and the dark red area represents tissue in which restimulation would result in action potentials with normal upstrokes. The dark red area is termed an *excitable gap*. In functionally defined, or "leading circle," reentry (bottom), there is no anatomic pathway and no excitable gap. Rather, the circulating wavefront creates an area of inexcitable tissue at its core. In this type of reentry, the circuit does not necessarily remain in the same anatomic position during consecutive beats. During mapping of excitation sequences in the heart, this type of activity may be manifest as one or more "rotors."

arrhythmias, whereas the most likely approach for terminating functionally determined reentry is prolongation of refractoriness (Knollmann and Roden, 2008; Priori et al., 1999; Task Force, 1991). In atrial and ventricular myocytes, refractoriness can be prolonged by delaying the recovery of Na^+ channels from inactivation. Drugs that act by blocking Na^+ channels generally shift the voltage dependence of recovery from block (Figure 30–5B) and so prolong refractoriness (Figure 30–11).

Drugs that increase action potential duration without direct action on Na^+ channels (e.g., by blocking delayed rectifier currents) also will prolong refractoriness (Figure 30–11). Particularly in SA or AV nodal tissues, Ca^{2+} channel blockade prolongs refractoriness. Drugs that interfere with cell-cell coupling also theoretically should increase refractoriness in multicellular preparations; *amiodarone*, a drug with a multiplicity of electrophysiologic actions that may be antiarrhythmic, may exert this effect in diseased tissue. Acceleration of conduction in an area of slow conduction also could inhibit reentry; *lidocaine* may exert such an effect, and peptides that suppress experimental arrhythmias by increasing gap junction conductance have been described. Arrhythmia-prone hearts often display abnormal anatomy and histology, notably enhanced fibrosis, and some evidence suggests anti-inflammatory or antifibrotic interventions could thus be antiarrhythmic by preventing these changes (Van Wagoner et al., 2015).

State-Dependent Ion Channel Block

Knowing the structural and molecular determinants of ion channel permeation and drug block has provided key information for analyzing the actions of available and new antiarrhythmic compounds (MacKinnon, 2003). A key concept is that ion channel–blocking drugs bind to specific sites on the ion channel proteins to modify function (e.g., decrease current). The affinity of the ion channel protein for the drug on its target site generally varies as the ion channel protein shuttles among functional conformations (or ion channel "states"; see Figure 30–2). Physicochemical characteristics, such as molecular weight and lipid solubility, are important determinants of this state-dependent binding. State-dependent binding has been studied most extensively in the case of Na^+ channel–blocking drugs. Most useful agents of this type block open or inactivated Na^+ channels and have little affinity for channels in the resting state. Most Na^+ channel blockers bind to a local anesthetic binding site in the pore of Nav1.5 (Fozzard et al., 2005). Thus, during each action potential, drugs bind to Na^+ channels and block them, and with each diastolic interval, drugs dissociate, and the block is released. Allosteric mechanisms have also been described whereby drug binding to a site distant from the pore nevertheless alters channel conformation and thus permeation though the pore.

As illustrated in Figure 30–12, the dissociation rate is a key determinant of steady-state block of Na^+ channels. When heart rate increases, the time available for dissociation decreases, and steady-state Na^+ channel block increases. The rate of recovery from block also slows as cells are depolarized, as in ischemia. This explains the finding that Na^+ channel blockers depress Na^+ current, and hence conduction, to a greater extent in ischemic tissues than in normal tissues. Open- versus inactivated-state block also may be important in determining the effects of some drugs. Increased action potential duration, which results in a relative increase in time spent in the inactivated state, may increase block by drugs that bind to inactivated channels, such as lidocaine or amiodarone.

The rate of recovery from block often is expressed as a time constant ($\tau_{recovery}$, the time required to complete approximately 63% of an exponentially determined process to be complete). In the case of drugs such as lidocaine, $\tau_{recovery}$ is so short (<<1 sec) that recovery from block is very rapid, and substantial Na^+ channel block occurs only in rapidly driven tissues, particularly in ischemia. Conversely, drugs such as *flecainide* have such long $\tau_{recovery}$ values (>10 sec) that roughly the same numbers of Na^+ channels are blocked during systole and diastole. As a result, slowing of conduction occurs even in normal tissues at normal rates.

Classifying Antiarrhythmic Drugs

Classifying drugs by common electrophysiological properties emphasizes the connection between basic electrophysiological actions and antiarrhythmic effects (Vaughan Williams, 1992). To the extent that the clinical actions of drugs can be predicted from their basic electrophysiological properties, such classification schemes have merit. However, as each compound is better characterized in a range of in vitro and in vivo test systems, it becomes apparent that differences in pharmacological effects occur even among drugs that share the same classification, some of which may be responsible for the observed clinical differences in responses to drugs of the same broad "class" (Table 30–3).

An alternative way of approaching antiarrhythmic therapy is to attempt to classify arrhythmia mechanisms and then to target drug therapy to the electrophysiological mechanism most likely to terminate or prevent the arrhythmia (Priori et al., 1999; Task Force, 1991) (Table 30–2). This approach has been further enhanced by an increasing understanding of arrhythmia mechanisms in genetic diseases such as LQTS and CPVT, so a genetic framework represents a complementary approach for improving antiarrhythmic drug development and therapy (Knollmann and Roden, 2008).

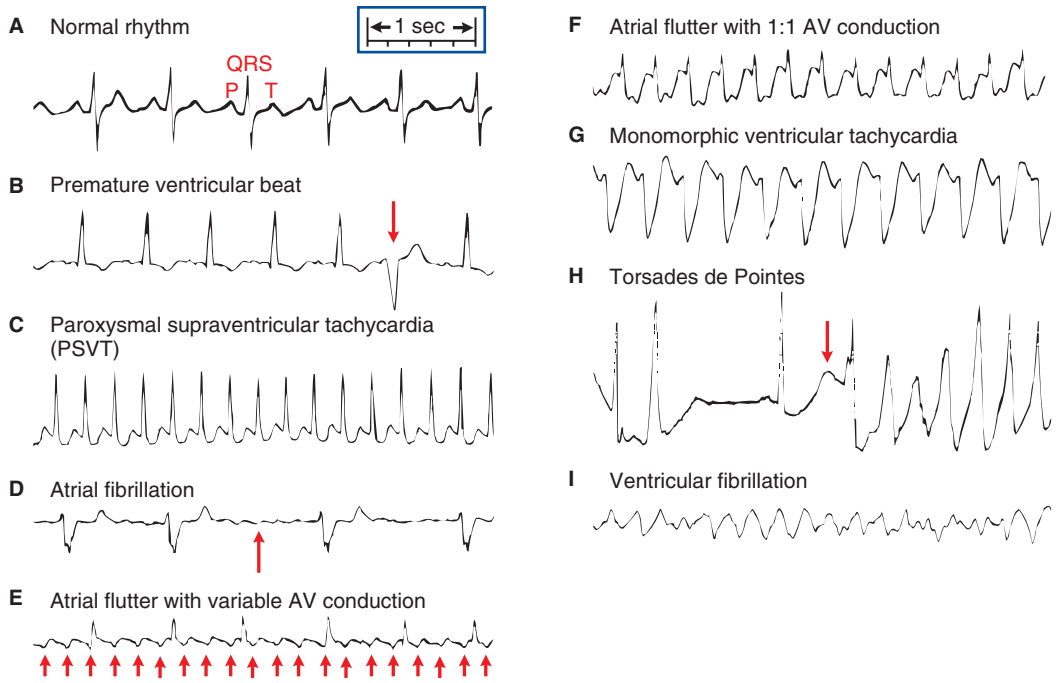


Figure 30–9 *Electrocardiograms showing normal and abnormal cardiac rhythms.* The P, QRS, and T waves in normal sinus rhythm are shown in panel **A**. Panel **B** shows a premature beat arising in the ventricle (arrow). PSVT is shown in panel **C**; this is most likely reentry using an accessory pathway (see Figure 30–7) or reentry within or near the AV node. In atrial fibrillation (panel **D**), there are no P waves, and the QRS complexes occur irregularly (and at a slow rate in this example); electrical activity between QRS complexes shows small undulations (arrow) corresponding to fibrillatory activity in the atria. In atrial flutter (panel **E**), the atria beat rapidly, approximately 250 beats/min (arrows) in this example, and the ventricular rate is variable. If a drug that slows the rate of atrial flutter is administered, 1:1 AV conduction (panel **F**) can occur. In monomorphic VT (panel **G**), identical wide QRS complexes occur at a regular rate, 180 beats per min. The electrocardiographic features of the torsades de pointes syndrome (panel **H**) include a very long QT interval (>600 ms in this example, arrow) and VT in which each successive beat has a different morphology (polymorphic VT). Panel **I** shows the disorganized electrical activity characteristic of VF.

Na^+ Channel Block

The extent of Na^+ channel block depends critically on heart rate and membrane potential, as well as on drug-specific physicochemical characteristics that determine $\tau_{recovery}$ (Figure 30–12). The description that follows applies when Na^+ channels are blocked, that is, at rapid heart rates in diseased tissue with a rapid-recovery drug such as *lidocaine* or even at normal rates in normal tissues with a slow-recovery drug such as *flecainide*. When Na^+ channels are blocked, threshold for excitability is decreased; that is, greater membrane depolarization is required to open enough Na^+ channels to overcome K^+ currents at the resting membrane potential and elicit an action potential. This change in threshold probably contributes to the clinical finding that Na^+ channel blockers tend to increase both pacing threshold and the energy required to defibrillate the fibrillating heart. These deleterious effects may be important if antiarrhythmic drugs are used in patients with pacemakers or implanted defibrillators. Na^+ channel block decreases conduction velocity in nonnodal tissue and increases QRS duration. Usual doses of flecainide prolong QRS intervals by 25% or more during normal rhythm, whereas lidocaine increases QRS intervals only at very fast heart rates. Drugs with $\tau_{recovery}$ values greater than 10 sec (e.g., *flecainide*) also tend to prolong the PR interval; it is not known whether this represents additional Ca^{2+} channel block (see discussion that follows) or block of fast-response tissue in the region of the AV node. Drug effects on the PR interval also are highly modified by autonomic effects. For example, *quinidine* actually tends to shorten the PR interval largely as a result of its vagolytic properties. Action potential duration is either unaffected or is shortened by Na^+ channel block; some Na^+ channel–blocking drugs do prolong cardiac action potentials but by other mechanisms, usually K^+ channel block (Table 30–3).

By increasing threshold, Na^+ channel block decreases automaticity (Figure 30–10B) and can inhibit triggered activity arising from DADs or EADs. Many Na^+ channel blockers also decrease phase 4 slope (Figure 30–10A). In anatomically defined reentry, Na^+ channel blockers may decrease conduction sufficiently to extinguish the propagating reentrant wavefront. However, as described previously, conduction slowing owing to Na^+ channel block may exacerbate reentry. Block of Na^+ channels also shifts the voltage dependence of recovery from inactivation (Figure 30–5B) to more negative potentials, thereby tending to increase refractoriness. Thus, whether a given drug exacerbates or suppresses reentrant arrhythmias depends on the balance between its effects on refractoriness and on conduction in a particular reentrant circuit. *Lidocaine* and *mexiletine* have short $\tau_{recovery}$ values and are not useful in atrial fibrillation or flutter, whereas *quinidine*, *flecainide*, *propafenone*, and similar agents are effective in some patients. Many of these agents owe part of their antiarrhythmic activity to blockade of K^+ channels.

Na^+ Channel Blocker Toxicity

Conduction slowing in potential reentrant circuits can account for toxicity of drugs that block the Na^+ channel (Table 30–1). For example, Na^+ channel block decreases conduction velocity and hence slows atrial flutter rate. Normal AV nodal function permits a greater number of impulses to penetrate the ventricle, and heart rate actually may increase (Figure 30–9). Thus, with Na^+ channel blocker therapy, atrial flutter rate may drop from 300 per min, with 2:1 or 4:1 AV conduction (i.e., a heart rate of 150 or 75 beats per min), to 220 per min, but with 1:1 transmission to the ventricle (i.e., a heart rate of 220 beats per min), with potentially disastrous consequences. This form of drug-induced arrhythmia is especially common during treatment with quinidine because the drug also increases AV nodal conduction through its vagolytic properties; flecainide, propafenone, and occasionally amiodarone also have been implicated. Therapy with Na^+ channel blockers in patients with reentrant ventricular tachycardia after a myocardial infarction can increase the frequency and severity of arrhythmic episodes. Although the mechanism is unclear, slowed conduction allows the reentrant wavefront to persist within the tachycardia circuit. Such drug-exacerbated arrhythmia can be difficult to

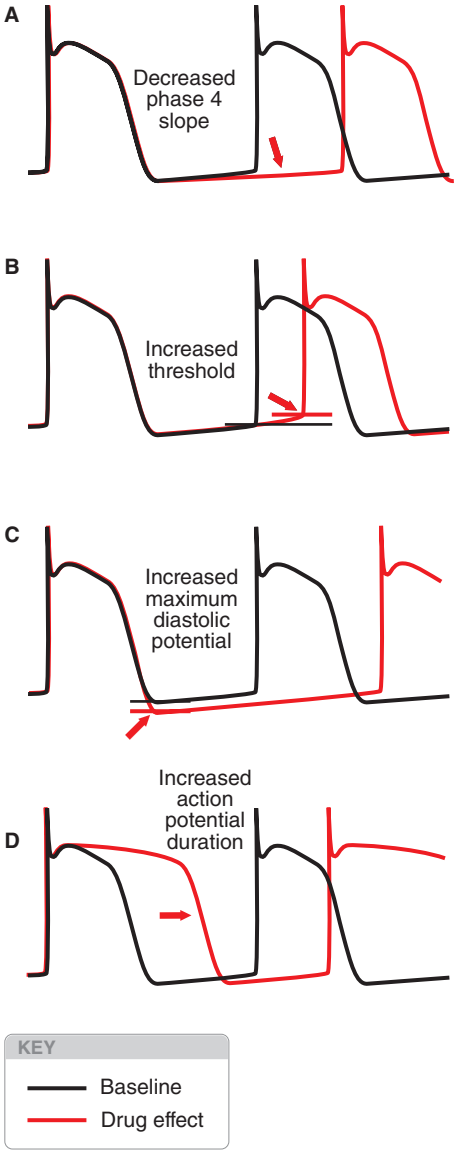


Figure 30–10 *Four ways to reduce the rate of spontaneous discharge.* The horizontal lines in panels **B** and **C** mark the threshold potentials for triggering an action potential before and after drug application.

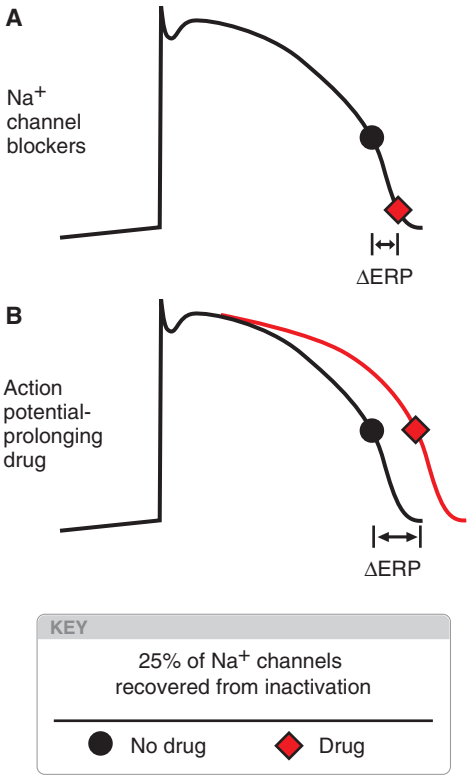


Figure 30–11 *Two ways to increase refractoriness.* In this figure, the black dot indicates the point at which a sufficient number of Na^+ channels (an arbitrary 25%; see Figure 30–5B) have recovered from inactivation to allow a premature stimulus to produce a propagated response in the absence of a drug. Block of Na^+ channels (**A**) shifts voltage dependence of recovery (see Figure 30–5B) and so delays the point at which 25% of channels have recovered (red diamond), prolonging the ERP. Note that if the drug also dissociates slowly from the channel (see Figure 30–12), refractoriness in fast-response tissues actually can extend beyond full repolarization ("postrepolarization refractoriness"). Drugs that prolong the action potential (**B**) also will extend the point at which an arbitrary percentage of Na^+ channels have recovered from inactivation, even without directly interacting with Na^+ channels.

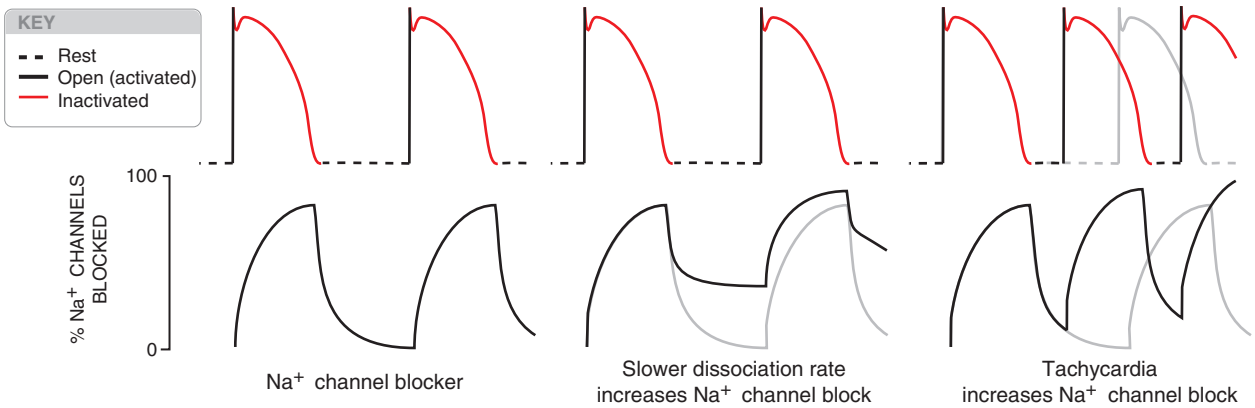


Figure 30–12 *Recovery from block of Na^+ channels during diastole.* This recovery is the critical factor determining extent of steady-state Na^+ channel block. Na^+ channel blockers bind to (and block) Na^+ channels in the open or inactivated states, resulting in phasic changes in the extent of block during the action potential. As shown in the middle panel, a decrease in the rate of recovery from block increases the extent of block. Different drugs have different rates of recovery, and depolarization reduces the rate of recovery. The right panel shows that increasing heart rate, which results in relatively less time spent in the rest state and also increases the extent of block. (Reproduced with permission from Roden DM, et al. Clinical pharmacology of antiarrhythmic agents. In: Josephson ME, ed. *Sudden Cardiac Death*. Blackwell Scientific, London, **1993**, 182–185.)

TABLE 30–3 ■ MAJOR ELECTROPHYSIOLOGIC ACTIONS OF ANTIARRHYTHMIC DRUGS

DRUG	Na^+ CHANNEL BLOCK		↑APD	Ca^{2+} CHANNEL BLOCK	AUTONOMIC EFFECTS	OTHER EFFECTS
	$\tau_{RECOVERY}$[1], *SECONDS*	STATE DEPENDENCE[1]				
Lidocaine	0.1	I > O				
Phenytoin	0.2	I				
Mexiletine[a]	0.3					
Procainamide	1.8	O	√		Ganglionic blockade (especially intravenous)	√: Metabolite prolongs APD
Quinidine	3	O	√	(x)	α Blockade, vagolytic Anticholinergic	
Disopyramide[b]	9	O	√		Anticholinergic	
Propafenone[b]	11	O ≈ I	√		β Blockade (variable clinical effect)	√ RyR2 channel block
Flecainide[a]	11	O	(x)	(x)		
β Blockers: Propanolol[b]					β Blockade	Na^+ channel block in vitro
Sotalol[b]			√		β Blockade	
Amiodarone, dronedarone	1.6	I	√	(x)	Noncompetitive β blockade	Antithyroid action
Dofetilide			√			
Ibutilide			√			
Verapamil[a]				√		
Diltiazem[a]				√		
Digoxin					√: Vagal stimulation	√: Inhibition of Na^+, K^+-ATPase
Adenosine					√: Adenosine receptor activation	√: Activation of outward K^+ current
Magnesium				?√		Mechanism not well understood

√Indicates an effect that is important in mediating the clinical action of a drug. (x)Indicates a demonstrable effect whose relationship to drug action in patients is less well established. [a]Indicates drugs prescribed as racemates, and the enantiomers are thought to exert similar electrophysiologic effects. [b]Indicates racemates for which clinically relevant differences in the electrophysiologic properties of individual enantiomers have been reported (see text). One approach to classifying drugs is:

Class	*Major action*
I	Na^+ channel block
II	β blockade
III	action potential prolongation (usually by K^+ channel block)
IV	Ca^{2+} channel block

Drugs are listed here according to this scheme. It is important to bear in mind, however, that many drugs exert multiple effects that contribute to their clinical actions. It is occasionally clinically useful to subclassify Na^+ channel blockers by their rates of recovery from drug-induced block ($\tau_{recovery}$) under physiologic conditions. Because this is a continuous variable and can be modulated by factors such as depolarization of the resting potential, these distinctions can become blurred: class Ib, $\tau_{recovery}$ <1 s; class Ia, $\tau_{recovery}$ 1–10 s; class Ic, $\tau_{recovery}$ >10 s. These class and subclass effects are associated with distinctive ECG changes, characteristic "class" toxicities, and efficacy in specific arrhythmia syndromes (see text). [1]These data are dependent on experimental conditions, including species and temperature. The $\tau_{recovery}$ values cited here are from Courtney (1987). O, open-state blocker; I, inactivated-state blocker.

manage, and deaths owing to intractable drug-induced ventricular tachycardia have been reported. In this setting, Na^+ infusion may be beneficial. Drug-exacerbated ventricular tachycardia or VF also likely accounts for increased mortality with Na^+ channel blockers compared to placebo in patients convalescing from acute myocardial infarction in the CAST (Echt et al., 1991). Several Na^+ channel blockers (e.g., *procainamide* and quinidine) have been reported to exacerbate neuromuscular paralysis by D-tubocurarine (see Chapter 11).

Action Potential Prolongation

Most drugs that prolong the action potential do so by blocking I_{Kr} (Roden et al., 1993), although increased late Na^+ current also produces this effect (Lu et al., 2012; Yang et al., 2014). Both drug effects increase action potential duration and reduce normal automaticity (Figure 30–10D). Increased action potential duration, seen as an increase in QT interval, increases refractoriness (Figure 30–11) and therefore should be an effective way of treating reentry (Task Force, 1991). Experimentally, K^+ channel block produces a series of desirable effects: reduced defibrillation energy requirement, inhibition of VF owing to acute ischemia, and increased contractility (Roden, 1993; Singh, 1993). As shown in Table 30–3, many K^+ channel–blocking drugs also interact with β adrenergic receptors (sotalol) or other channels (e.g., amiodarone and quinidine). Amiodarone and sotalol appear to be at least as effective as drugs with predominant Na^+ channel–blocking properties in both atrial and ventricular arrhythmias. "Pure" action potential–prolonging drugs (e.g., dofetilide and ibutilide) also are available (Murray, 1998; Torp-Pedersen et al., 1999).

Toxicity of Drugs That Prolong the Action Potential

Most of these agents disproportionately prolong cardiac action potentials and the QT interval when underlying heart rate is slow and can cause torsades de pointes (Table 30–1, Figure 30–9). While this effect usually is seen with QT-prolonging antiarrhythmic drugs, it can occur more rarely

with drugs that are used for noncardiac indications. For such agents, the risk of torsades de pointes may become apparent only after widespread use postmarketing, and recognition of this risk has been a common cause for drug withdrawal (Roden, 2004). Sex hormones modify cardiac ion channels and help account for the clinically observed increased incidence of drug-induced torsades de pointes in women (Tadros et al., 2014).

Ca^{2+} Channel Block

The major electrophysiological effects resulting from block of cardiac Ca^{2+} channels are in nodal tissues. Dihydropyridines, such as nifedipine, which are used commonly in angina and hypertension (see Chapters 27 and 28), preferentially block Ca^{2+} channels in vascular smooth muscle; their cardiac electrophysiological effects, such as heart rate acceleration, result principally from reflex sympathetic activation secondary to peripheral vasodilation. Only verapamil, diltiazem, and bepridil (no longer available in the U.S.) block Ca^{2+} channels in cardiac cells at clinically used doses. These drugs generally slow heart rate (Figure 30–10A), although hypotension, if marked, can cause reflex sympathetic activation and tachycardia. The velocity of AV nodal conduction decreases, so the PR interval increases. AV nodal block occurs as a result of decremental conduction, as well as increased AV nodal refractoriness. These effects form the basis of the antiarrhythmic actions of Ca^{2+} channel blockers in reentrant arrhythmias whose circuit involves the AV node, such as AV reentrant tachycardia (Figure 30–7).

Another important indication for antiarrhythmic therapy is to reduce the ventricular rate in atrial flutter or fibrillation. Parenteral verapamil and diltiazem are approved for temporary control of rapid ventricular rate in atrial flutter or fibrillation and for rapid conversion of PSVT to sinus rhythm (where their use has largely been supplanted by adenosine). Oral verapamil or diltiazem may be used to control the ventricular rate in chronic atrial flutter or fibrillation and for prophylaxis of repetitive PSVT. Unlike β blockers, Ca^{2+} channel blockers have not been shown to reduce mortality after myocardial infarction (Singh, 1990). In contrast to other Ca^{2+} channel blockers, bepridil increases action potential duration in many tissues and can exert an antiarrhythmic effect in atria and ventricles. However, because bepridil can cause torsades de pointes, it is not prescribed widely and has been discontinued in the U.S.

Verapamil and Diltiazem

The major adverse effect of intravenous verapamil or diltiazem is hypotension, particularly with bolus administration. This was a particular problem when the drugs were used mistakenly in patients with ventricular tachycardia (in which Ca^{2+} channel blockers usually are not effective) misdiagnosed as PSVT; the drugs are now rarely used for this indication. Hypotension also is frequent in patients receiving other vasodilators and in patients with underlying left ventricular dysfunction, which the drugs can exacerbate. Severe sinus bradycardia or AV block also occurs, especially in susceptible patients, such as those also receiving β blockers. With oral therapy, these adverse effects tend to be less severe. Constipation can occur with oral verapamil.

Verapamil is prescribed as a racemate. L-Verapamil is the more potent Ca^{2+} channel blocker. However, with oral therapy, the L-enantiomer undergoes more extensive first-pass hepatic metabolism. For this reason, a given concentration of verapamil prolongs the PR interval to a greater extent when administered intravenously (where concentrations of the L- and D-enantiomers are equivalent) than when administered orally. Diltiazem also undergoes extensive first-pass hepatic metabolism, and both drugs have metabolites that exert Ca^{2+} channel–blocking actions. In clinical practice, adverse effects during therapy with verapamil or diltiazem are determined largely by underlying heart disease and concomitant therapy; plasma concentrations of these agents are not measured routinely. Both drugs can increase serum digoxin concentration, although the magnitude of this effect is variable; excess slowing of ventricular response may occur in patients with atrial fibrillation.

Blockade of β Adrenergic Receptors

β Adrenergic stimulation increases the magnitude of the Ca^{2+} current and slows its inactivation; increases the magnitude of the repolarizing current I_{Ks}; increases pacemaker current (thereby increasing sinus rate; DiFrancesco, 1993); increases the Ca^{2+} stored in the SR (thereby increasing likelihood of spontaneous Ca^{2+} release and DADs); and under pathophysiological conditions, can increase both DAD- and EAD-mediated arrhythmias. The increases in plasma epinephrine associated with severe stress (e.g., acute myocardial infarction or resuscitation after cardiac arrest) lower serum K^+, especially in patients receiving chronic diuretic therapy. β blockers inhibit these effects and can be antiarrhythmic by reducing heart rate, decreasing intracellular Ca^{2+} overload, and inhibiting afterdepolarization-mediated automaticity. Epinephrine-induced hypokalemia appears to be mediated by β_2 adrenergic receptors and is blocked by "noncardioselective" antagonists such as propranolol (see Chapter 12). In acutely ischemic tissue, β blockers increase the energy required to fibrillate the heart, an antiarrhythmic action. These effects may contribute to the reduced short-term and long-term mortality observed in trials of chronic therapy with β blockers—after myocardial infarction (Singh, 1990).

As with Ca^{2+} channel blockers and digitalis, β blockers increase AV nodal conduction time (increased PR interval) and prolong AV nodal refractoriness; hence, they are useful in terminating reentrant arrhythmias that involve the AV node and in controlling ventricular response in atrial fibrillation or flutter. In many (but not all) patients with the congenital LQTS, in all patients with the CPVT syndrome, as well as in many other patients, arrhythmias are triggered by physical or emotional stress; β blockers may be useful in these cases (Roden and Spooner, 1999; Schwartz et al., 2000). β blockers also reportedly are effective in controlling arrhythmias owing to Na^+ channel blockers; this effect may be due in part to slowing of the heart rate, which then decreases the extent of rate-dependent conduction slowing by Na^+ channel block.

Adverse effects of β blockade include fatigue, bronchospasm, hypotension, impotence, depression, aggravation of heart failure, worsening of symptoms owing to peripheral vascular disease, and masking of the symptoms of hypoglycemia in diabetic patients (see Chapter 12). In patients with arrhythmias owing to excess sympathetic stimulation (e.g., pheochromocytoma or *clonidine* withdrawal), β blockers can result in unopposed α adrenergic stimulation, with resulting severe hypertension or α adrenergic–mediated arrhythmias. In such patients, arrhythmias should be treated with both α and β blockers or with a drug such as labetalol that combines α- and β-blocking properties. Abrupt discontinuation of chronic β-blocker therapy can lead to "rebound" symptoms, including hypertension, increased angina, and arrhythmias; thus, β blockers are tapered over 2 weeks prior to discontinuation of chronic therapy (see Chapters 12 and 27–29).

Selected β Blockers

It is likely that most β blockers share antiarrhythmic properties. Some, such as propranolol, also exert Na^+ channel–blocking effects at high concentrations. Similarly, drugs with intrinsic sympathomimetic activity may be less useful as antiarrhythmics (Singh, 1990). Acebutolol is as effective as quinidine in suppressing ventricular ectopic beats, an arrhythmia that many clinicians no longer treat. Sotalol (see its discussion in a separate section) is more effective for many arrhythmias than other β blockers, probably because of its K^+ channel–blocking actions. Esmolol (see separate discussion that follows) is a β_1-selective agent that has a very short elimination half-life. Intravenous esmolol is useful in clinical situations in which immediate β adrenergic blockade is desired. Some β blockers (e.g., propranolol) are CYP2D6 substrates; thus, efficacy may vary across individuals (Chapter 7). Many clinicians now favor nadolol when β blockade is needed in congenital arrhythmias (CPVT, LQTS).

Principles in the Clinical Use of Antiarrhythmic Drugs

Drugs that modify cardiac electrophysiology often have a very narrow margin between the doses required to produce a desired effect and those associated with adverse effects. Moreover, antiarrhythmic drugs can induce new arrhythmias with possibly fatal consequences. Nonpharmacological

treatments, such as cardiac pacing, electrical defibrillation, or ablation of targeted regions, are indicated for some arrhythmias; in other cases, no therapy is required, even though an arrhythmia is detected. Therefore, the fundamental principles of therapeutics described here must be applied to optimize antiarrhythmic therapy.

1. Identify and Remove Precipitating Factors

Factors that commonly precipitate cardiac arrhythmias include hypoxia, electrolyte disturbances (especially hypokalemia), myocardial ischemia, and certain drugs. Antiarrhythmics, including cardiac glycosides, are not the only drugs that can precipitate arrhythmias (Table 30–1). For example, *theophylline* can cause multifocal atrial tachycardia, which sometimes can be managed simply by reducing the dose of theophylline. Torsades de pointes can arise during therapy not only with action potential–prolonging antiarrhythmics but also with other "noncardiovascular" drugs not ordinarily classified as having effects on ion channels (Roden, 2004). The incidence can vary from 1% to 3% in patients receiving sotalol or dofetilide to very rare (<1/50,000) with some noncardiovascular drugs. Drugs with a very wide range of clinical indications have been implicated: These include some antibiotics (including antibacterials, antiprotozoals, antivirals, and antifungals), antipsychotics, antihistamines, antidepressants, and methadone. The website https://crediblemeds.org maintains a list of drugs (and levels of evidence) that have been implicated in this adverse effect.

2. Establish the Goals of Treatment

Some Arrhythmias Should Not Be Treated: The CAST Example

Abnormalities of cardiac rhythm are readily detectable by a variety of recording methods. However, the mere detection of an abnormality does not equate with the need for therapy. This was illustrated in CAST. The presence of asymptomatic ventricular ectopic beats is a known marker for increased risk of sudden death owing to VF in patients convalescing from myocardial infarction. In CAST, patients whose ventricular ectopic beats were suppressed by the potent Na^+ channel blocker encainide (no longer marketed) or flecainide were randomly assigned to receive those drugs or placebo. Unexpectedly, the mortality rate was 2- to 3-fold higher among patients treated with the drugs than those treated with placebo (Echt et al., 1991). While the explanation for this effect is not known, several lines of evidence suggest that, in the presence of these drugs, transient episodes of myocardial ischemia or sinus tachycardia can cause marked conduction slowing (because these drugs have a very long $\tau_{recovery}$), resulting in fatal reentrant ventricular tachyarrhythmias.

One consequence of this pivotal clinical trial was to reemphasize the concept that therapy should be initiated only when a clear benefit to the patient can be identified. When symptoms are obviously attributable to an ongoing arrhythmia, there usually is little doubt that termination of the arrhythmia will be beneficial; when chronic therapy is used to prevent recurrence of an arrhythmia, the risks may be greater (Roden, 1994). *Among the antiarrhythmic drugs discussed here, only β adrenergic blockers and, to a lesser extent, amiodarone* (Connolly, 1999) *demonstrably reduce mortality during long-term therapy.*

Symptoms Due to Arrhythmias

Some patients with an arrhythmia may be asymptomatic; in this case, establishing any benefit for treatment will be difficult. Some patients may present with presyncope, syncope, or even cardiac arrest, which may be due to brady- or tachyarrhythmias. Other patients may present with a sensation of irregular heartbeats (i.e., palpitations) that can be minimally symptomatic in some individuals and incapacitating in others. The irregular heartbeats may be due to intermittent premature contractions or to sustained arrhythmias such as atrial fibrillation (which results in an irregular ventricular rate) (Figure 30–9). Finally, patients may present with symptoms owing to decreased cardiac output attributable to arrhythmias. The most common symptom is breathlessness either at rest or on exertion. Occasionally, sustained or frequent tachycardias may produce no "arrhythmia" symptoms (such as palpitations) but will depress contractile function; these patients may present with heart failure due to "tachycardia-induced cardiomyopathy", a condition that can be controlled by treating the arrhythmia.

Choosing Among Therapeutic Approaches

In choosing among available therapeutic options, it is important to establish clear therapeutic goals. For example, three options are available in patients with atrial fibrillation: (1) reduce the ventricular response using AV nodal-blocking agents such as digitalis, verapamil, diltiazem, or β blockers (Table 30–1); (2) restore and maintain normal rhythm using drugs such as flecainide or amiodarone; or (3) decide not to implement antiarrhythmic therapy, especially if the patient truly is asymptomatic. Most patients with atrial fibrillation also benefit from anticoagulation to reduce stroke incidence regardless of symptoms (Dzeshka and Lip, 2015) (see Chapter 32).

Factors that contribute to choice of therapy include not only symptoms but also the type and extent of structural heart disease, the QT interval prior to drug therapy, the coexistence of conduction system disease, and the presence of noncardiac diseases (Table 30–4). In the rare patient with the WPW syndrome and atrial fibrillation, the ventricular response can be extremely rapid and can be accelerated paradoxically with digitalis or Ca^{2+} channel blockers; deaths owing to drug therapy have been reported under these circumstances.

The frequency and reproducibility of arrhythmia should be established prior to initiating therapy because inherent variability in the occurrence of arrhythmias can be confused with a beneficial or adverse drug effect. Techniques for this assessment include recording cardiac rhythm for prolonged periods or evaluating the response of the heart to artificially induced premature beats. It is important to recognize that drug therapy may be only partially effective. A marked decrease in the duration

TABLE 30–4 ■ PATIENT-SPECIFIC ANTIARRHYTHMIC DRUG CONTRAINDICATIONS

CONDITION	EXCLUDE/USE WITH CAUTION
Cardiac	
Heart failure	Disopyramide, flecainide
Sinus or AV node dysfunction	Digoxin, verapamil, diltiazem, β blockers, amiodarone
Wolff–Parkinson–White syndrome (risk of extremely rapid rate if atrial fibrillation develops)	Digoxin, verapamil, diltiazem
Infranodal conduction disease	Na^+ channel blockers, amiodarone
Aortic/subaortic stenosis	Bretylium
History of myocardial infarction	Flecainide
Prolonged QT interval	Quinidine, procainamide, disopyramide, sotalol, dofetilide, ibutilide, amiodarone
Cardiac transplant	Adenosine
Noncardiac	
Diarrhea	Quinidine
Prostatism, glaucoma	Disopyramide
Arthritis	Chronic procainamide
Lung disease	Amiodarone
Tremor	Mexiletine
Constipation	Verapamil
Asthma, peripheral vascular disease, hypoglycemia	β blockers, propafenone

of paroxysms of atrial fibrillation may be sufficient to render a patient asymptomatic even if an occasional episode still can be detected.

3. Minimize Risks

Antiarrhythmic Drugs Can Cause Arrhythmias

One well-recognized risk of antiarrhythmic therapy is the possibility of provoking new arrhythmias, with potentially life-threatening consequences. Antiarrhythmic drugs can provoke arrhythmias by different mechanisms (Table 30–1). These drug-provoked arrhythmias must be recognized because further treatment with antiarrhythmic drugs often exacerbates the problem, whereas withdrawal of the causative agent is curative. Thus, establishing a precise diagnosis is critical, and targeting therapies at underlying mechanisms of the arrhythmias may be required. For example, treating a ventricular tachycardia with verapamil not only may be ineffective but also can cause catastrophic cardiovascular collapse.

Monitoring of Plasma Concentration

Some adverse effects of antiarrhythmic drugs result from excessive plasma drug concentrations. Measuring plasma concentration and adjusting the dose to maintain the concentration within a prescribed therapeutic range may minimize some adverse effects. In many patients, serious adverse reactions relate to interactions involving antiarrhythmic drugs (often at usual plasma concentrations), transient factors such as electrolyte disturbances or myocardial ischemia, and the type and extent of the underlying heart disease (Roden, 1994). Factors such as generation of unmeasured active metabolites, variability in elimination of enantiomers (which may exert differing pharmacological effects), and disease- or enantiomer-specific abnormalities in drug binding to plasma proteins can complicate the interpretation of plasma drug concentrations.

Patient-Specific Contraindications

Another way to minimize the adverse effects of antiarrhythmic drugs is to avoid certain drugs in certain patient subsets altogether. For example, patients with a history of congestive heart failure are particularly prone to develop heart failure during *disopyramide* therapy. In other cases, adverse effects of drugs may be difficult to distinguish from exacerbations of underlying disease. Amiodarone may cause interstitial lung disease; its use therefore is undesirable in a patient with advanced pulmonary disease in whom the development of this potentially fatal adverse effect would be difficult to detect. Specific diseases that constitute relative or absolute contraindications to specific drugs are listed in Table 30–4.

4. Consider the Electrophysiology of the Heart as a "Moving Target"

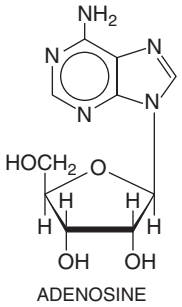
Cardiac electrophysiology varies dynamically in response to external influences such as changing autonomic tone, myocardial ischemia, and myocardial stretch (Priori et al., 1999). For example, myocardial ischemia results in changes in extracellular K^+ that make the resting potential less negative, inactivate Na^+ channels, decrease Na^+ current, and slow conduction. In addition, myocardial ischemia can result in the formation and release of metabolites such as lysophosphatidylcholine, which can alter ion channel function; ischemia also may activate channels that otherwise are quiescent, such as the ATP-inhibited K^+ channels. Thus, in response to myocardial ischemia, a normal heart may display changes in resting potential, conduction velocity, intracellular Ca^{2+} concentrations, and repolarization, any one of which then may create arrhythmias or alter response to antiarrhythmic therapy.

Antiarrhythmic Drugs

Summaries of important electrophysiological and pharmacokinetic features of the drugs considered here are presented in Tables 30–3 and 30–5. Ca^{2+} channel blockers and β blockers are discussed in Chapters 12 and 27 to 29. The drugs are presented in alphabetical order. Prescribing patterns have changed over the past several decades in part because fewer suppliers market older drugs, such as quinidine or procainamide, which are therefore increasingly difficult to obtain, a problem for a small number of patients who may still benefit from treatment (Inama et al., 2010; Viskin et al., 2013).

Adenosine

Adenosine is a naturally occurring nucleoside that is administered as a rapid intravenous bolus for the acute termination of reentrant supraventricular arrhythmias (Link, 2012). Rare cases of ventricular tachycardia in patients with otherwise-normal hearts are thought to be DAD mediated and can be terminated by adenosine. Adenosine also has been used to produce controlled hypotension during some surgical procedures and in the diagnosis of coronary artery disease. Intravenous ATP appears to produce effects similar to those of adenosine.



ADENOSINE

Pharmacological Effects

The effects of adenosine are mediated by its interaction with specific G protein–coupled adenosine receptors. Adenosine activates acetylcholine-sensitive K^+ current in the atrium and sinus and AV nodes, resulting in shortening of action potential duration, hyperpolarization, and slowing of normal automaticity (Figure 30–10C). Adenosine also inhibits the electrophysiological effects of increased intracellular cyclic AMP that occur with sympathetic stimulation. Because adenosine thereby reduces Ca^{2+} currents, it can be antiarrhythmic by increasing AV nodal refractoriness and by inhibiting DADs elicited by sympathetic stimulation.

Administration of an intravenous bolus of adenosine to humans transiently slows sinus rate and AV nodal conduction velocity and increases AV nodal refractoriness. A bolus of adenosine can produce transient sympathetic activation by interacting with carotid baroreceptors; a continuous infusion can cause hypotension.

Adverse Effects

A major advantage of adenosine therapy is that adverse effects are short-lived because the drug is transported into cells and deaminated so rapidly. Transient asystole (lack of any cardiac rhythm whatsoever) is common but usually lasts less than 5 sec and is in fact the therapeutic goal. Most patients feel a sense of chest fullness and dyspnea when therapeutic doses (6 to 12 mg) of adenosine are administered. Rarely, an adenosine bolus can precipitate atrial fibrillation, presumably by heterogeneously shortening atrial action potentials, or bronchospasm.

Clinical Pharmacokinetics

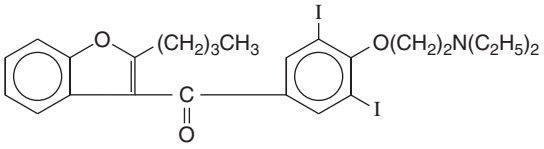
Adenosine is eliminated with a half-life of seconds by carrier-mediated uptake, which occurs in most cell types, including the endothelium, followed by metabolism by adenosine deaminase. Adenosine probably is the only drug whose efficacy requires a rapid bolus dose, preferably through a large central intravenous line; slow administration results in elimination of the drug prior to its arrival at the heart.

The effects of adenosine are potentiated in patients receiving *dipyridamole*, an adenosine-uptake inhibitor, and in patients with cardiac transplants owing to denervation hypersensitivity. Methylxanthines (see Tables 14-7, 40-2, and 40-3, and Figure 40-5) such as theophylline and caffeine block adenosine receptors; therefore, larger-than-usual doses are required to produce an antiarrhythmic effect in patients who have consumed these agents in beverages or as therapy.

Amiodarone

Amiodarone exerts a multiplicity of pharmacological effects, none of which is clearly linked to its arrhythmia-suppressing properties. Amiodarone is a structural analogue of thyroid hormone, and some of its antiarrhythmic

actions and its toxicity may be attributable to interaction with nuclear thyroid hormone receptors. Amiodarone is highly lipophilic, is concentrated in many tissues, and is eliminated extremely slowly; consequently, adverse effects may resolve very slowly. In the U.S., the drug is indicated for oral therapy in patients with recurrent ventricular tachycardia or VF resistant to other drugs. In addition, the intravenous form is a first-line drug for management of ventricular tachycardia or VF causing cardiac arrest (Dorian et al., 2002). Trials of oral amiodarone have shown a modest beneficial effect on mortality after acute myocardial infarction (Amiodarone Trials Meta-Analysis Investigators, 1997). Despite uncertainties about its mechanisms of action and the potential for serious toxicity, amiodarone is used widely in the treatment of common arrhythmias such as atrial fibrillation (Roy et al., 2000).



AMIODARONE

Pharmacological Effects

Studies of the acute effects of amiodarone in in vitro systems are complicated by its insolubility in water, necessitating the use of solvents such as dimethyl sulfoxide, which can have electrophysiological effects on its own. Amiodarone's effects may be mediated by perturbation of the lipid environment of the ion channels. Amiodarone blocks inactivated Na^+ channels and has a relatively rapid rate of recovery (time constant ≈ 1.6 sec) from block. It also decreases Ca^{2+} current and transient outward delayed rectifier and inward rectifier K^+ currents and exerts a noncompetitive adrenergic-blocking effect. Amiodarone potently inhibits abnormal automaticity and, in most tissues, prolongs action potential duration. Amiodarone decreases conduction velocity by Na^+ channel block and by a poorly understood effect on cell-cell coupling that may be especially important in diseased tissue. Prolongations of the PR, QRS, and QT intervals and sinus bradycardia are frequent during chronic therapy. Amiodarone prolongs refractoriness in all cardiac tissues; Na^+ channel block, delayed repolarization owing to K^+ channel block, and inhibition of cell-cell coupling all may contribute to this effect.

Adverse Effects

Hypotension owing to vasodilation and depressed myocardial performance are frequent with the intravenous form of amiodarone and may be due in part to the solvent. While depressed contractility can occur during long-term oral therapy, it is unusual. Despite administration of high doses that would cause serious toxicity if continued long term, adverse effects are unusual during oral drug-loading regimens, which typically require several weeks. Occasional patients develop nausea during the loading phase, which responds to a decrease in daily dose.

Adverse effects during long-term therapy reflect both the size of daily maintenance doses and the cumulative dose, suggesting that tissue accumulation may be responsible. The most serious adverse effect during chronic amiodarone therapy is pulmonary fibrosis, which can be rapidly progressive and fatal. Underlying lung disease, doses of 400 mg/d or more, and recent pulmonary insults such as pneumonia appear to be risk factors. Serial chest X-rays or pulmonary function studies may detect early amiodarone toxicity, but monitoring plasma concentrations has not been useful. With low doses, such as 200 mg/d or less as used in atrial fibrillation, pulmonary toxicity is less common (Zimetbaum, 2007). Other adverse effects during long-term therapy include corneal microdeposits (which often are asymptomatic), hepatic dysfunction, neuromuscular symptoms (most commonly peripheral neuropathy or proximal muscle weakness), photosensitivity, and hypo- or hyperthyroidism. The multiple effects of amiodarone on thyroid function are discussed further in Chapter 43. Treatment consists of withdrawal of the drug and supportive measures, including corticosteroids, for life-threatening pulmonary toxicity; reduction of dosage may be sufficient if the drug is deemed necessary and the adverse effect is not life threatening. Despite the marked QT prolongation and bradycardia typical of chronic amiodarone therapy, torsades de pointes and other drug-induced tachyarrhythmias are unusual.

Clinical Pharmacokinetics

Amiodarone's oral bioavailability is about 30%, presumably due to poor absorption. This incomplete bioavailability is important in calculating equivalent dosing regimens when converting from intravenous to oral therapy. The drug distributes into lipid; heart tissue-to-plasma concentration ratios of greater than 20:1 and lipid-to-plasma ratios of greater than 300:1 have been reported. After the initiation of amiodarone therapy, increases in refractoriness, a marker of pharmacological effect, require several weeks to develop. Amiodarone undergoes hepatic metabolism by CYP3A4 to desethyl-amiodarone, a metabolite with pharmacological effects similar to those of the parent drug. When amiodarone therapy is withdrawn from a patient who has been receiving therapy for several years, plasma concentrations decline with a half-life of weeks to months. The mechanisms of amiodarone and desethyl-amiodarone elimination are not well established.

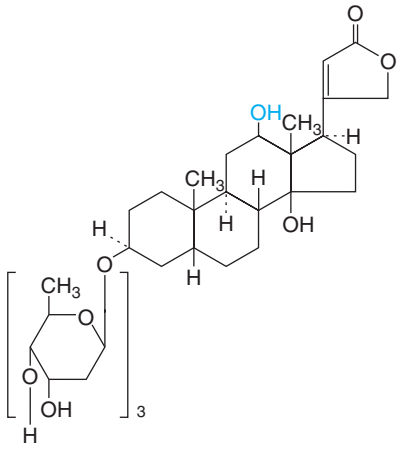
A therapeutic plasma amiodarone concentration range of 0.5 to 2 μg/mL has been proposed. However, efficacy apparently depends as much on duration of therapy as on plasma concentration, and elevated plasma concentrations do not predict toxicity. Because of amiodarone's slow accumulation in tissue, a high-dose oral loading regimen (e.g., 800 to 1600 mg/d) usually is administered for several weeks before maintenance therapy is started. The maintenance dose is adjusted based on adverse effects and the arrhythmias being treated. If the presenting arrhythmia is life threatening, dosages of more than 300 mg/d normally are used unless unequivocal toxicity occurs. On the other hand, maintenance doses of 200 mg/d or less are used if recurrence of an arrhythmia would be tolerated, as in patients with atrial fibrillation, because amiodarone slows the ventricular rate during atrial fibrillation.

Dosage adjustments are not required in hepatic, renal, or cardiac dysfunction. Amiodarone potently inhibits the hepatic metabolism or renal elimination of many compounds. Mechanisms identified to date include inhibition of CYP3A4, CYP2C9, and P-glycoprotein (see Chapters 5 and 6). Dosages of warfarin, other antiarrhythmics (e.g., flecainide, procainamide, and quinidine), or digoxin usually require reduction during amiodarone therapy.

Bretylium

Bretylium is a quaternary ammonium compound that prolongs cardiac action potentials and interferes with reuptake of norepinephrine by sympathetic neurons. In the past, bretylium was used to treat VF and prevent its recurrence; the drug is currently not available in the U.S.

Digoxin



DIGOXIN

Pharmacological Effects

Digitalis glycosides exert positive inotropic effects and have been used in heart failure; now, they are rarely prescribed (see Chapter 29). Their inotropic action results from increased intracellular Ca^{2+}, which also forms the basis for arrhythmias related to cardiac glycoside intoxication. Cardiac glycosides increase phase 4 slope (i.e., increase the rate of automaticity), especially if $[K]_o$ is low. These drugs (e.g., digoxin) also exert prominent vagotonic actions, resulting in inhibition of Ca^{2+} currents in the AV node and activation of acetylcholine-mediated K^+ currents in the atrium. Thus, the major "indirect" electrophysiological effects of cardiac glycosides are hyperpolarization, shortening of atrial action potentials, and increases in AV nodal refractoriness. The last action accounts for the utility of digoxin in terminating reentrant arrhythmias involving the AV node and in controlling ventricular response in patients with atrial fibrillation. Cardiac glycosides may be especially useful in the last situation because many such patients have heart failure, which can be exacerbated by other AV nodal–blocking drugs such as Ca^{2+} channel blockers or β blockers. However, sympathetic drive is increased markedly in many patients with advanced heart failure, so digitalis is not very effective in decreasing the rate; on the other hand, even a modest decrease in rate can ameliorate heart failure.

Similarly, in other conditions in which high sympathetic tone drives rapid AV conduction (e.g., chronic lung disease and thyrotoxicosis), digitalis therapy may be only marginally effective in slowing the rate. In heart transplant patients, in whom innervation has been ablated, cardiac glycosides are ineffective for rate control. Increased sympathetic activity and hypoxia can potentiate digitalis-induced changes in automaticity and DADs, thus increasing the risk of digitalis toxicity. A further complicating feature in thyrotoxicosis is increased digoxin clearance.

The major ECG effects of cardiac glycosides are PR prolongation and a nonspecific alteration in ventricular repolarization (manifested by depression of the ST segment), whose underlying mechanism is not well understood.

Adverse Effects

Because of the low therapeutic index of cardiac glycosides, their toxicity is a common clinical problem (see Chapter 29). Arrhythmias, nausea, disturbances of cognitive function, and blurred or yellow vision are the usual manifestations. Elevated serum concentrations of digitalis, hypoxia (e.g., owing to chronic lung disease), and electrolyte abnormalities (e.g., hypokalemia, hypomagnesemia, and hypercalcemia) predispose patients to digitalis-induced arrhythmias. While digitalis intoxication can cause virtually any arrhythmia, certain types of arrhythmias are characteristic. Arrhythmias that should raise a strong suspicion of digitalis intoxication are those in which DAD-related tachycardias occur along with impairment of sinus node or AV nodal function. Atrial tachycardia with AV block is classic, but ventricular bigeminy (sinus beats alternating with beats of ventricular origin), "bidirectional" ventricular tachycardia (a rare entity), AV junctional tachycardias, and various degrees of AV block also can occur. With severe intoxication (e.g., with suicidal ingestion), severe hyperkalemia owing to poisoning of Na^+, K^+–ATPase and profound bradyarrhythmias, which may be unresponsive to pacing therapy, are seen. In patients with elevated serum digitalis levels, the risk of precipitating VF by DC cardioversion probably is increased; in those with therapeutic blood levels, DC cardioversion can be used safely.

Minor forms of cardiac glycoside intoxication may require no specific therapy beyond monitoring cardiac rhythm until symptoms and signs of toxicity resolve. Sinus bradycardia and AV block often respond to intravenous atropine, but the effect is transient. Mg^{2+} has been used successfully in some cases of digitalis-induced tachycardia. Any serious arrhythmia should be treated with antidigoxin Fab fragments (Digibind, Digifab), which are highly effective in binding digoxin and digitoxin and greatly enhance their renal excretion (see Chapter 29). Serum glycoside concentrations rise markedly with antidigitalis antibodies, but these represent bound (pharmacologically inactive) drug. Temporary cardiac pacing may be required for advanced sinus node or AV node dysfunction. Digitalis exerts direct arterial vasoconstrictor effects, which can be especially deleterious in patients with advanced atherosclerosis who receive intravenous drug; mesenteric and coronary ischemia have been reported.

Clinical Pharmacokinetics

The only digitalis glycoside used in the U.S. is digoxin. Digitoxin (various generic preparations) also is used for chronic oral therapy outside the U.S. Digoxin tablets are incompletely (75%) bioavailable. In some patients, intestinal microflora may metabolize digoxin, markedly reducing bioavailability. In these patients, higher-than-usual doses are required for clinical efficacy; toxicity is a serious risk if antibiotics are administered that destroy intestinal microflora. Inhibition of P-glycoprotein (see further discussion) also may play a role in cases of toxicity. Digoxin is 20% to 30% protein bound.

The antiarrhythmic effects of digoxin can be achieved with intravenous or oral therapy. However, digoxin undergoes relatively slow distribution to effector site(s); therefore, even with intravenous therapy, there is a lag of several hours between drug administration and the development of measurable antiarrhythmic effects such as PR interval prolongation or slowing of the ventricular rate in atrial fibrillation. To avoid intoxication, a loading dose of approximately 0.6 to 1 mg digoxin is administered over 24 h. Measurement of postdistribution serum digoxin concentration and adjustment of the daily dose (0.0625 to 0.5 mg) to maintain concentrations of 0.5 to 2 ng/mL are useful during chronic digoxin therapy (Table 30–5). Some patients may require and tolerate higher concentrations, but with an increased risk of adverse effects.

The elimination half-life of digoxin ordinarily is about 36 h, so maintenance doses are administered once daily. Renal elimination of unchanged drug accounts for about 80% of digoxin elimination. Digoxin doses should be reduced (or dosing interval increased) and serum concentrations monitored closely in patients with impaired excretion owing to renal failure or in patients who are hypothyroid. Digitoxin undergoes primarily hepatic metabolism and may be useful in patients with fluctuating or advanced renal dysfunction. Digitoxin metabolism is accelerated by drugs such as phenytoin and rifampin that induce hepatic metabolism. Digitoxin's elimination half-life is even longer than that of digoxin (about 7 days); it is highly protein bound, and its therapeutic range is 10 to 30 ng/mL.

Amiodarone, quinidine, verapamil, diltiazem, cyclosporine, itraconazole, propafenone, and flecainide decrease digoxin clearance, likely by inhibiting P-glycoprotein, the major route of digoxin elimination (Fromm et al., 1999). New steady-state digoxin concentrations are approached after four to five half-lives (i.e., in about a week). Digitalis toxicity results so often with quinidine or amiodarone that it is routine to decrease the dose of digoxin if these drugs are started. In all cases, digoxin concentrations should be measured regularly and the dose adjusted if necessary. Hypokalemia, which can be caused by many drugs (e.g., diuretics, amphotericin B, and corticosteroids), will potentiate digitalis-induced arrhythmias.

Disopyramide

Disopyramide exerts electrophysiological effects very similar to those of quinidine, but the drugs have different adverse effect profiles. Disopyramide can be used to maintain sinus rhythm in patients with atrial flutter or atrial fibrillation and to prevent recurrence of ventricular tachycardia or VF. Because of its negative inotropic effects, it is sometimes used in hypertrophic cardiomyopathy. Disopyramide is prescribed as a racemate.

Pharmacological Actions and Adverse Effects

The in vitro electrophysiological actions of *S*-(+)-disopyramide are similar to those of quinidine. The *R*-(–)-enantiomer produces similar Na^+ channel block but does not prolong cardiac action potentials. Unlike quinidine, racemic disopyramide does not antagonize α adrenergic receptors, but does exert prominent anticholinergic actions that account for many of its adverse effects. These include precipitation of glaucoma, constipation, dry mouth, and urinary retention; the last is most common in males with prostatism but also can occur in females. Disopyramide can cause torsades de pointes and also commonly depresses contractility, which can precipitate heart failure. In patients with hypertrophic cardiomyopathy, this depression contractility may be exploited to therapeutic

advantage to decrease dynamic outflow tract obstruction (Sherrid and Arabadjian, 2012).

Clinical Pharmacokinetics

Disopyramide is well absorbed. Binding to plasma proteins is concentration dependent, so a small increase in total concentration may represent a disproportionately larger increase in free drug concentration. Disopyramide is eliminated by both hepatic metabolism (to a weakly active metabolite) and renal excretion of unchanged drug. The dose should be reduced in patients with renal dysfunction. Higher-than-usual dosages may be required in patients receiving drugs that induce hepatic metabolism, such as phenytoin.

Dofetilide

Dofetilide prolongs action potentials and the QT interval by potently blocking the I_{Kr} channel. Increased late Na^+ current, likely due to inhibition of phosphoinositide 3–kinase (Yang et al., 2014), may also contribute. The drug has virtually no extracardiac pharmacological effects. Dofetilide is effective in maintaining sinus rhythm in patients with atrial fibrillation. In the DIAMOND studies (Torp-Pedersen et al., 1999), dofetilide did not affect mortality in patients with advanced heart failure or in those convalescing from acute myocardial infarction. Dofetilide currently is available through a restricted distribution system that includes only physicians, hospitals, and other institutions that have received special educational programs covering proper dosing and in-hospital treatment initiation.

Adverse Effects

Torsades de pointes occurred in 1%–3% of patients in clinical trials where strict exclusion criteria (e.g., hypokalemia) were applied and continuous ECG monitoring was used to detect marked QT prolongation in the hospital. Other adverse effects were no more common than with placebo during premarketing clinical trials.

Clinical Pharmacokinetics

Most of a dose of dofetilide is excreted unchanged by the kidneys. In patients with mild-to-moderate renal failure, decreases in dosage based on creatinine clearance are required to minimize the risk of torsades de pointes. The drug should not be used in patients with advanced renal failure or with inhibitors of renal cation transport. Dofetilide also undergoes minor hepatic metabolism.

Dronedarone

Dronedarone is a noniodinated benzofuran derivative of amiodarone that is FDA-approved for the treatment of atrial fibrillation and atrial flutter. In randomized placebo-controlled trials, it was effective in maintaining sinus rhythm and reducing the ventricular response rate during episodes of atrial fibrillation (Patel et al., 2009). Compared to amiodarone, dronedarone treatment is associated with significantly fewer adverse events, but it is also significantly less effective in maintaining sinus rhythm. Dronedarone decreased hospital admissions compared to placebo in patients with a history of atrial fibrillation (Hohnloser et al., 2009). In other studies, however, the drug increased mortality in patients with permanent atrial fibrillation (Connolly et al., 2011) and in those with severe heart failure (Kober et al., 2008).

Pharmacological Effects

Like amiodarone, dronedarone is a blocker of multiple ion currents, including the rapidly activating delayed-rectifier K^+ current (I_{Kr}), the slowly activating delayed-rectifier K^+ current (I_{Ks}), the inward rectifier K^+ current (I_{K1}), the acetylcholine-activated K^+ current, the peak Na^+ current, and the L-type Ca^{2+} current. It has stronger antiadrenergic effects than amiodarone.

Adverse Effects and Drug Interactions

The most common adverse reactions are diarrhea, nausea, abdominal pain, vomiting, and asthenia. Dronedarone causes dose-dependent prolongation of the QTc interval, but torsades de pointes is rare. Dronedarone is metabolized by CYP3A and is a moderate inhibitor of CYP3A, CYP2D6, and P-glycoprotein. Potent CYP3A4 inhibitors such as ketoconazole may increase dronedarone exposure by as much as 25-fold. Consequently, dronedarone should not be coadministered with potent CYP3A4 inhibitors (e.g., antifungals, macrolide antibiotics). Coadministration with other drugs metabolized by CYP2D6 (e.g., metoprolol) or P-glycoprotein (e.g., digoxin) may result in increased drug concentrations. Dronedarone may cause severe liver injury; the FDA recommends monitoring of hepatic enzymes.

Esmolol

Esmolol is a β_1-selective agent that is metabolized by erythrocyte esterases and so has a very short elimination half-life (9 min). Intravenous esmolol is useful in clinical situations in which immediate β adrenergic blockade is desired (e.g., for rate control of rapidly conducted atrial fibrillation). Because of esmolol's very rapid elimination, adverse effects due to β adrenergic blockade—should they occur—dissipate rapidly when the drug is stopped. Although methanol is a metabolite of esmolol, methanol intoxication has not been a clinical problem. The pharmacology of esmolol is described in further detail in Chapter 12.

Flecainide

The effects of flecainide therapy are thought to be attributable to the drug's very long $\tau_{recovery}$ from Na^+ channel block. Suppression of DADs triggered by RyR2 Ca^{2+} release may also contribute to flecainide's antiarrhythmic effect. In CAST, flecainide increased mortality in patients convalescing from myocardial infarction (Echt et al., 1991). However, it continues to be approved for certain arrhythmias in patients in whom structural heart disease is absent (Henthorn et al., 1991); this includes the maintenance of sinus rhythm in patients with supraventricular arrhythmias, including atrial fibrillation, as well as life-threatening ventricular arrhythmias, such as sustained ventricular tachycardia. Clinical case series suggested long-term flecainide efficacy in two congenital ventricular arrhythmia syndromes: type 3 LQTS due to mutations that cause late Na^+ currents and CPVT due to mutations that cause "leaky" RyR2 SR Ca^{2+} release channels. Supported by data from a recent randomized clinical trial (Kannankeril et al. 2017), flecainide has become the drug of choice for preventing arrhythmias in CPVT patients uncontrolled by β blockers.

Pharmacological Effects

Flecainide blocks Na^+ current and delayed rectifier K^+ current (I_{Kr}) in vitro at similar concentrations, 1 to 2 μM. It also blocks Ca^{2+} currents in vitro. Action potential duration is shortened in Purkinje cells, probably owing to block of late-opening Na^+ channels, but is prolonged in ventricular cells, probably owing to block of delayed rectifier current. Flecainide does not cause EADs in vitro but has been associated with rare cases of torsades de pointes. In atrial tissue, flecainide disproportionately prolongs action potentials at fast rates, an especially desirable antiarrhythmic drug effect; this effect contrasts with that of quinidine, which prolongs atrial action potentials to a greater extent at slower rates. Flecainide prolongs the duration of PR, QRS, and QT intervals even at normal heart rates. Flecainide is also an open channel blocker of RyR2 Ca^{2+} release channels and prevents arrhythmogenic Ca^{2+} release from the SR and hence DADs in isolated myocytes (Hilliard et al., 2010). The RyR2 channel block by flecainide targets directly the underlying molecular defect in patients with mutations in the RyR2 gene and the cardiac calsequestrin gene, which may explain why flecainide suppresses ventricular arrhythmias in patients with CPVT refractory to β blocker therapy (Watanabe et al., 2009; Kannankeril et al, 2017).

Adverse Effects

Flecainide produces few subjective complaints in most patients; dose-related blurred vision is the most common noncardiac adverse effect. It can exacerbate congestive heart failure in patients with depressed left ventricular performance. The most serious adverse effects are provocation or exacerbation of potentially lethal arrhythmias. These include acceleration of ventricular rate in patients with atrial flutter, increased frequency of episodes of reentrant ventricular tachycardia, and increased mortality in patients convalescing from myocardial infarction. As discussed previously, it is likely that all these effects can be attributed to Na^+

channel block. Flecainide also can cause heart block in patients with conduction system disease.

Clinical Pharmacokinetics

Flecainide is well absorbed. The elimination $t_{1/2}$ is shorter with urinary acidification (10 h) than with urinary alkalinization (17 h), but it is nevertheless sufficiently long to allow dosing twice daily (Table 30–5). Elimination occurs by both renal excretion of unchanged drug and hepatic metabolism to inactive metabolites. The latter is mediated by the polymorphically distributed enzyme CYP2D6. However, even in patients in whom this pathway is absent because of genetic polymorphism or inhibition by other drugs (e.g., quinidine or fluoxetine), renal excretion ordinarily is sufficient to prevent drug accumulation. In the rare patient with renal dysfunction and lack of active CYP2D6, flecainide may accumulate to toxic plasma concentrations. Flecainide is a racemate, but there are no differences in the electrophysiological effects or disposition kinetics of its enantiomers. Some reports have suggested that plasma flecainide concentrations greater than 1 μg/mL should be avoided to minimize the risk of flecainide toxicity; however, in susceptible patients, the adverse electrophysiological effects of flecainide therapy can occur at therapeutic plasma concentrations.

Ibutilide

Ibutilide is an I_{Kr} blocker that in some systems also activates an inward Na^+ current (Murray, 1998). The action potential–prolonging effect of the drug may arise from either mechanism. Ibutilide is administered as a rapid infusion (1 mg over 10 min) for the immediate conversion of atrial fibrillation or flutter to sinus rhythm. The drug's efficacy rate is higher in patients with atrial flutter (50%-70%) than in those with atrial fibrillation (30%–50%). In atrial fibrillation, the conversion rate is lower in those in whom the arrhythmia has been present for weeks or months compared with those in whom it has been present for days. The major toxicity with ibutilide is torsades de pointes, which occurs in up to 6% of patients and requires immediate cardioversion in up to one-third of these. The drug undergoes extensive first-pass metabolism, so it is not used orally. It is eliminated by hepatic metabolism and has a $t_{1/2}$ of 2–12 h (average 6 h).

Lidocaine

Lidocaine is a local anesthetic that also is useful in the acute intravenous therapy of ventricular arrhythmias. When lidocaine was administered to all patients with suspected myocardial infarction, the incidence of VF was reduced. However, survival to hospital discharge tended to be decreased, perhaps because of lidocaine-exacerbated heart block or congestive heart failure. Therefore, lidocaine no longer is administered routinely to all patients in coronary care units.

Pharmacological Effects

Lidocaine blocks both open and inactivated cardiac Na^+ channels. In vitro studies suggested that lidocaine-induced block reflects an increased likelihood that the Na^+ channel protein assumes a nonconducting conformation in the presence of drug (Balser et al., 1996). Recovery from block is rapid, so lidocaine exerts greater effects in depolarized (e.g., ischemic) or rapidly driven tissues. Lidocaine is not useful in atrial arrhythmias, possibly because atrial action potentials are so short that the Na^+ channel is in the inactivated state only briefly compared with diastolic (recovery) times, which are relatively long. In some studies, lidocaine increased current through inward rectifier channels, but the clinical significance of this effect is not known. Lidocaine can hyperpolarize Purkinje fibers depolarized by low $[K]_o$ or stretch; the resulting increased conduction velocity may be antiarrhythmic in reentry.

Lidocaine decreases automaticity by reducing the slope of phase 4 and altering the threshold for excitability. Action potential duration usually is unaffected or is shortened; such shortening may be due to block of the few Na^+ channels that inactivate late during the cardiac action potential. Lidocaine usually exerts no significant effect on PR or QRS duration; QT is unaltered or slightly shortened. The drug exerts little effect on hemodynamic function, although rare cases of lidocaine-associated exacerbations of heart failure have been reported, especially in patients with very poor left ventricular function. For additional information on lidocaine, see Chapter 22 on local anesthetics.

Adverse Effects

When a large intravenous dose of lidocaine is administered rapidly, seizures can occur. When plasma concentrations of the drug rise slowly above the therapeutic range, as may occur during maintenance therapy, tremor, dysarthria, and altered levels of consciousness are more common. Nystagmus is an early sign of lidocaine toxicity.

Clinical Pharmacokinetics

Lidocaine is well absorbed but undergoes extensive though variable first-pass hepatic metabolism; thus, oral use of the drug is inappropriate. In theory, therapeutic plasma concentrations of lidocaine may be maintained by intermittent intramuscular administration, but the intravenous route is preferred (Table 30–5). Lidocaine's metabolites, GX and monoethyl GX, are less potent as Na^+ channel blockers than the parent drug. GX and lidocaine appear to compete for access to the Na^+ channel, suggesting that with infusions during which GX accumulates, lidocaine's efficacy may be diminished. With infusions lasting longer than 24 h, the clearance of lidocaine falls—an effect that may result from competition between parent drug and metabolites for access to hepatic drug-metabolizing enzymes.

Plasma concentrations of lidocaine decline biexponentially after a single intravenous dose, indicating that a multicompartment model is necessary to analyze lidocaine disposition. The initial drop in plasma lidocaine following intravenous administration occurs rapidly, with a $t_{1/2}$ of about 8 min, and represents distribution from the central compartment to peripheral tissues. The terminal elimination $t_{1/2}$ of about 2 h represents drug elimination by hepatic metabolism. Lidocaine's efficacy depends on maintenance of therapeutic plasma concentrations in the central compartment. Therefore, the administration of a single bolus dose of lidocaine can result in transient arrhythmia suppression that dissipates rapidly as the drug is distributed and concentrations in the central compartment fall. To avoid this distribution-related loss of efficacy, a loading regimen of 3 to 4 mg/kg over 20–30 min is used (e.g., an initial 100 mg followed by 50 mg every 8 min for three doses). Subsequently, stable concentrations can be maintained in plasma with an infusion of 1 to 4 mg/min, which replaces drug removed by hepatic metabolism. The time to steady-state lidocaine concentrations is approximately 8–10 h. If the maintenance infusion rate is too low, arrhythmias may recur hours after the institution of apparently successful therapy. On the other hand, if the rate is too high, toxicity may result. In either case, routine measurement of plasma lidocaine concentration at the time of expected steady state is useful in adjusting maintenance infusion rate.

In heart failure, the central volume of distribution is decreased, so the total loading dose should be decreased. Because lidocaine clearance also is decreased, the rate of the maintenance infusion should be decreased. Lidocaine clearance also is reduced in hepatic disease, during treatment with *cimetidine* or β blockers, and during prolonged infusions. Frequent measurement of plasma lidocaine concentration and dose adjustment to ensure that plasma concentrations remain within the therapeutic range (1.5 to 5 μg/mL) are necessary to minimize toxicity in these settings. Lidocaine is bound to the acute-phase reactant α_1-acid glycoprotein. Diseases such as acute myocardial infarction are associated with increases in α_1-acid glycoprotein and protein binding and hence a decreased proportion of free drug. These findings may explain why some patients require and tolerate higher-than-usual total plasma lidocaine concentrations to maintain antiarrhythmic efficacy.

Magnesium

The intravenous administration of 1 to 2 g $MgSO_4$ reportedly is effective in preventing recurrent episodes of torsades de pointes, even if the serum Mg^{2+} concentration is normal (Brugada, 2000). However, controlled studies of this effect have not been performed. The mechanism of action is unknown because the QT interval is not shortened; an effect on the inward current,

possibly a Ca^{2+} current, responsible for the triggered upstroke arising from EADs (black arrow, Figure 30–6B) is possible. Intravenous Mg^{2+} also has been used successfully in arrhythmias related to digitalis intoxication.

Large placebo-controlled trials of intravenous Mg^{2+} to improve outcome in acute myocardial infarction have yielded conflicting results (ISIS-4 Collaborative Group, 1995; Woods and Fletcher, 1994). While oral Mg^{2+} supplements may be useful in preventing hypomagnesemia, there is no evidence that chronic Mg^{2+} ingestion exerts a direct antiarrhythmic action.

Mexiletine

Mexiletine is an analogue of lidocaine that has been modified to reduce first-pass hepatic metabolism and permit chronic oral therapy. The electrophysiological actions are similar to those of lidocaine. Tremor and nausea, the major dose-related adverse effects, can be minimized by taking the drugs with food.

Mexiletine undergoes hepatic metabolism, which is inducible by drugs such as phenytoin. Mexiletine is approved for treating ventricular arrhythmias; combinations of mexiletine with quinidine or sotalol may increase efficacy while reducing adverse effects. In vitro studies and clinical case series have suggested a role for mexiletine (or flecainide; see previous discussion) in correcting the aberrant late inward Na^+ current in type 3 congenital LQTS (Napolitano et al., 2006).

Procainamide

Procainamide is an analogue of the local anesthetic procaine (see Figure 22–1). It exerts electrophysiological effects similar to those of quinidine but lacks quinidine's vagolytic and α adrenergic blocking activity. Procainamide is better tolerated than quinidine when given intravenously. Loading and maintenance intravenous infusions are used in the acute therapy of many supraventricular and ventricular arrhythmias. However, long-term oral treatment is poorly tolerated and often is stopped owing to adverse effects.

Pharmacological Effects

Procainamide is a blocker of open Na^+ channels with an intermediate $\tau_{recovery}$ from block. It also prolongs cardiac action potentials in most tissues, probably by blocking outward K^+ current(s). Procainamide decreases automaticity, increases refractory periods, and slows conduction. The major metabolite, *N*-acetyl procainamide, lacks the Na^+ channel–blocking activity of the parent drug but is equipotent in prolonging action potentials. Because the plasma concentrations of *N*-acetyl procainamide often exceed those of procainamide, increased refractoriness and QT prolongation during chronic procainamide therapy may be partly attributable to the metabolite. However, it is the parent drug that slows conduction and produces QRS interval prolongation. Although hypotension may occur at high plasma concentrations, this effect usually is attributable to ganglionic blockade rather than to any negative inotropic effect, which is minimal.

Adverse Effects

Hypotension and marked slowing of conduction are major adverse effects of high concentrations (>10 μg/mL) of procainamide, especially during intravenous use. Dose-related nausea is frequent during oral therapy and may be attributable in part to high plasma concentrations of *N*-acetyl procainamide. Torsades de pointes can occur, particularly when plasma concentrations of *N*-acetyl procainamide rise to greater than 30 μg/mL. Procainamide produces potentially fatal bone marrow aplasia in 0.2% of patients; the mechanism is not known, but high plasma drug concentrations are not suspected.

During long-term therapy, most patients will develop biochemical evidence of the drug-induced lupus syndrome, such as circulating antinuclear antibodies. Therapy need not be interrupted merely because of the presence of antinuclear antibodies. However, 25%–50% of patients eventually develop symptoms of the lupus syndrome; common early symptoms are rash and small-joint arthralgias. Other symptoms of lupus, including pericarditis with tamponade, can occur, although renal involvement is unusual. The lupus-like symptoms resolve on cessation of therapy or during treatment with *N*-acetyl procainamide (see discussion that follows).

Clinical Pharmacokinetics

Procainamide is eliminated rapidly ($t_{1/2}$ ~ 3–4 h) by both renal excretion of unchanged drug and hepatic metabolism. The major pathway for hepatic metabolism is conjugation by *N*-acetyl transferase, whose activity is determined genetically, to form *N*-acetyl procainamide. *N*-Acetyl procainamide is eliminated by renal excretion ($t_{1/2}$ ~ 6–10 h) and is not significantly converted back to procainamide. Because of the relatively rapid elimination rates of both the parent drug and its major metabolite, oral procainamide usually is administered as a slow-release formulation. In patients with renal failure, procainamide or *N*-acetyl procainamide can accumulate to potentially toxic plasma concentrations. Reduction of procainamide dose and dosing frequency and monitoring of plasma concentrations of both compounds are required in this situation. Because the parent drug and metabolite exert different pharmacological effects, the past practice of using the sum of their concentrations to guide therapy is inappropriate.

In individuals who are "slow acetylators," the procainamide-induced lupus syndrome develops more often and earlier during treatment than among rapid acetylators. In addition, the symptoms of procainamide-induced lupus resolve during treatment with *N*-acetyl procainamide. Both these findings support results of in vitro studies suggesting that it is chronic exposure to the parent drug (or an oxidative metabolite) that results in the lupus syndrome; these findings also provided one rationale for the further development of *N*-acetyl procainamide and its analogues as antiarrhythmic agents (Roden, 1993).

Propafenone

Propafenone is a Na^+ channel blocker with a relatively slow time constant for recovery from block (Funck-Brentano et al., 1990). Some data suggest that, like flecainide, propafenone also blocks K^+ channels. Its major electrophysiological effect is to slow conduction in fast-response tissues. The drug is prescribed as a racemate; while the enantiomers do not differ in their Na^+ channel–blocking properties, *S*-(+)-propafenone is a β adrenergic receptor antagonist in vitro and in some patients. Propafenone prolongs PR and QRS durations. Chronic therapy with oral propafenone is used to maintain sinus rhythm in patients with supraventricular tachycardias, including atrial fibrillation; like other Na^+ channel blockers, it also can be used in ventricular arrhythmias, but with only modest efficacy. *R*-(−) propafenone blocks RyR2 channels and may be an alternative to flecainide in CPVT (Hwang et al, 2011).

Adverse Effects

Adverse effects during propafenone therapy include acceleration of ventricular response in patients with atrial flutter, increased frequency or severity of episodes of reentrant ventricular tachycardia, exacerbation of heart failure, and the adverse effects of β adrenergic blockade, such as sinus bradycardia and bronchospasm (see previous discussion and Chapter 12).

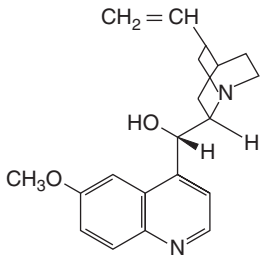
Clinical Pharmacokinetics

Propafenone is well absorbed and is eliminated primarily by CYP2D6-mediated hepatic metabolism (see Chapter 6). In most subjects ("extensive metabolizers"), propafenone undergoes extensive first-pass hepatic metabolism to 5-hydroxy propafenone, a metabolite equipotent to propafenone as a Na^+ channel blocker but much less potent as a β adrenergic receptor antagonist. A second metabolite, *N*-desalkyl propafenone, is formed by non-CYP2D6–mediated metabolism and is a less-potent blocker of Na^+ channels and β adrenergic receptors. CYP2D6-mediated metabolism of propafenone is saturable, so small increases in dose can increase plasma propafenone concentration disproportionately. In "poor metabolizer" subjects, in whom CYP2D6 activity is low or absent, first-pass hepatic metabolism is much less than in extensive metabolizers, and plasma propafenone concentrations will be much higher after an equal dose. The incidence of adverse effects during propafenone therapy is significantly higher in poor metabolizers.

CYP2D6 activity can be inhibited markedly by a number of drugs, including quinidine and fluoxetine. In extensive metabolizer subjects receiving such drugs or in poor metabolizer subjects, plasma propafenone concentrations of more than 1 μg/mL are associated with clinical effects of β adrenergic receptor blockade, such as reduction of exercise heart rate. It is recommended that dosage in patients with moderate-to-severe liver disease should be reduced to approximately 20%–30% of the usual dose, with careful monitoring. It is not known if propafenone doses must be decreased in patients with renal disease. A slow-release formulation allows twice-daily dosing.

Quinidine

As early as the 18th century, the bark of the cinchona plant was used to treat "rebellious palpitations" (Levy and Azoulay, 1994). Studies in the early 20th century identified quinidine, a diastereomer of the antimalarial quinine, as the most potent of the antiarrhythmic substances extracted from the cinchona plant, and by the 1920s, quinidine was used as an antiarrhythmic agent. Quinidine is used to maintain sinus rhythm in patients with atrial flutter or atrial fibrillation and to prevent recurrence of ventricular tachycardia or VF (Grace and Camm, 1998). Quinidine may be especially useful in preventing recurrent VF in unusual congenital arrhythmias syndromes such as Brugada syndrome or short QT syndrome (Inama et al., 2010; Viskin et al., 2013).



QUINIDINE

Pharmacological Effects

Quinidine blocks Na^+ current and multiple cardiac K^+ currents. It is an open-state blocker of Na^+ channels, with a $\tau_{recovery}$ in the intermediate (~3-sec) range; as a consequence, QRS duration increases modestly, usually by 10%–20%, at therapeutic dosages. At therapeutic concentrations, quinidine commonly prolongs the QT interval up to 25%, but the effect is highly variable. At concentrations as low as 1 μM, quinidine blocks Na^+ current and the rapid component of delayed rectifier (I_{Kr}); higher concentrations block the slow component of delayed rectifier, inward rectifier, transient outward current, and L-type Ca^{2+} current.

Quinidine's Na^+ channel–blocking properties result in an increased threshold for excitability and decreased automaticity. As a consequence of its K^+ channel–blocking actions, quinidine prolongs action potentials in most cardiac cells, most prominently at slow heart rates. In some cells, such as midmyocardial cells and Purkinje cells, quinidine consistently elicits EADs at slow heart rates, particularly when $[K]_o$ is low (Priori et al., 1999). Quinidine prolongs refractoriness in most tissues, probably as a result of both prolongation of action potential duration and Na^+ channel blockade.

In intact animals and humans, quinidine also produces α adrenergic receptor blockade and vagal inhibition. Thus, the intravenous use of quinidine is associated with marked hypotension and sinus tachycardia. Quinidine's vagolytic effects tend to inhibit its direct depressant effect on AV nodal conduction, so the effect of drug on the PR interval is variable. Moreover, quinidine's vagolytic effect can result in increased AV nodal transmission of atrial tachycardias such as atrial flutter (Table 30–1).

Adverse Effects

Noncardiac. Diarrhea is the most common adverse effect during quinidine therapy, occurring in 30%–50% of patients; the mechanism is not known. Diarrhea usually occurs within the first several days of quinidine therapy but can occur later. Diarrhea-induced hypokalemia may potentiate torsades de pointes due to quinidine.

A number of immunological reactions can occur during quinidine therapy. The most common is thrombocytopenia, which can be severe but which resolves rapidly with discontinuation of the drug. Hepatitis, bone marrow depression, and lupus syndrome occur rarely. None of these effects is related to elevated plasma quinidine concentrations.

Quinidine also can produce cinchonism, a syndrome that includes headache and tinnitus. In contrast to other adverse responses to quinidine therapy, cinchonism usually is related to elevated plasma quinidine concentrations and can be managed by dose reduction.

Cardiac. Of patients receiving quinidine therapy, 2%–8% will develop marked QT interval prolongation and torsades de pointes. In contrast to effects of sotalol, *N*-acetyl procainamide, and many other drugs, quinidine-associated torsades de pointes generally occurs at therapeutic or even subtherapeutic plasma concentrations. The reasons for individual susceptibility to this adverse effect are not known.

At high plasma concentrations of quinidine, marked Na^+ channel block can occur, with resulting ventricular tachycardia. This adverse effect occurs when very high doses of quinidine are used to try to convert atrial fibrillation to normal rhythm; this aggressive approach to quinidine dosing has been abandoned, and quinidine-induced ventricular tachycardia is unusual.

Quinidine can exacerbate heart failure or conduction system disease. However, in most patients with congestive heart failure, quinidine is well tolerated, perhaps because of its vasodilating actions.

Clinical Pharmacokinetics

Quinidine is well absorbed and is 80% bound to plasma proteins, including albumin and, like lidocaine, the acute-phase reactant α_1-acid glycoprotein. As with lidocaine, greater-than-usual doses (and total plasma quinidine concentrations) may be required to maintain therapeutic concentrations of free quinidine in high-stress states such as acute myocardial infarction. Quinidine undergoes extensive hepatic oxidative metabolism, and approximately 20% is excreted unchanged by the kidneys. One metabolite, 3-hydroxyquinidine, is nearly as potent as quinidine in blocking cardiac Na^+ channels and prolonging cardiac action potentials. Concentrations of unbound 3-hydroxyquinidine equal to or exceeding those of quinidine are tolerated by some patients. Other metabolites are less potent than quinidine, and their plasma concentrations are lower; thus, they are unlikely to contribute significantly to the clinical effects of quinidine.

There is substantial individual variability in the range of dosages required to achieve therapeutic plasma concentrations of 2 to 5 μg/mL. Some of this variability may be assay dependent because not all assays exclude quinidine metabolites. In patients with advanced renal disease or congestive heart failure, quinidine clearance is decreased only modestly. Thus, dosage requirements in these patients are similar to those in other patients.

Drug Interactions

Quinidine is a potent inhibitor of CYP2D6. As a result, the administration of quinidine to patients receiving drugs that undergo extensive CYP2D6-mediated metabolism may result in altered drug effects owing to accumulation of parent drug and failure of metabolite formation. For example, inhibition of CYP2D6-mediated metabolism of *codeine* to its active metabolite *morphine* results in decreased analgesia. On the other hand, inhibition of CYP2D6-mediated metabolism of propafenone results in elevated plasma propafenone concentrations and increased β adrenergic receptor blockade. Quinidine reduces the clearance of digoxin; inhibition of P-glycoprotein–mediated digoxin transport has been implicated (Fromm et al., 1999). Dextromethorphan, a CYP2D6 substrate that undergoes extensive first-pass bioinactivation, has shown promise in treatment of various neurological disorders, notably pseudobulbar affect. A combination of dextromethorphan and very low-dose quinidine (30 mg) inhibits the first-pass metabolism, achieves higher systemic concentrations than monotherapy, and is now approved for use in pseudobulbar affect (Olney and Rosen, 2010).

Quinidine metabolism is induced by drugs such as *phenobarbital* and phenytoin. In patients receiving these agents, very high doses of quinidine

may be required to achieve therapeutic concentrations. If therapy with the inducing agent is then stopped, quinidine concentrations may rise to very high levels, and its dosage must be adjusted downward. Cimetidine and verapamil also elevate plasma quinidine concentrations, but these effects usually are modest.

Sotalol

Sotalol is a nonselective β adrenergic receptor antagonist that also prolongs cardiac action potentials by inhibiting delayed rectifier and possibly other K^+ currents (Hohnloser and Woosley, 1994). Sotalol is prescribed as a racemate; the L-enantiomer is a much more potent β adrenergic receptor antagonist than the D-enantiomer, but the two are equipotent as K^+ channel blockers. In the U.S., sotalol is approved for use in patients with both ventricular tachyarrhythmias and atrial fibrillation or flutter. Clinical trials suggest that it is at least as effective as most Na^+ channel blockers in ventricular arrhythmias.

Sotalol prolongs action potential duration throughout the heart and QT interval on the ECG. It decreases automaticity, slows AV nodal conduction, and prolongs AV refractoriness by blocking both K^+ channels and β adrenergic receptors, but it exerts no effect on conduction velocity in fast-response tissue. Sotalol causes EADs and triggered activity in vitro and can cause torsades de pointes, especially when the serum K^+ concentration is low. Unlike the situation with quinidine, the incidence of torsades de pointes (1.5%–2% incidence) seems to depend on the dose of sotalol; indeed, torsades de pointes is the major toxicity with sotalol overdose. Occasional cases occur at low dosages, often in patients with renal dysfunction, because sotalol is eliminated by renal excretion of unchanged drug. The other adverse effects of sotalol therapy are those associated with β adrenergic receptor blockade (see previous discussion and Chapter 12).

Vernakalant

Vernakalant is an inhibitor of multiple ion channels and prolongs atrial refractory periods without significantly affecting ventricular refractoriness. Intravenous vernakalant has modest efficacy in terminating atrial fibrillation (Roy et al., 2008) and is available for this indication in several European countries, but not the U.S. Consult the 12th edition of this text for more information on this drug.

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Drug Facts for Your Personal Formulary: *Antiarrhythmic Agents*

Antiarrhythmic Drug	Therapeutic Uses	Major Toxicity and Clinical Pearls
Class IA: Na^+ Channel Blockers • Slow to intermediate off rate • Concomitant class III action (prolong QT)		
Procainamide	• Acute treatment of AF, VT, and VF • Chronic treatment to prevent AF, VT, and VF	• 40% of patients discontinue within 6 months of therapy due to side effects: hypotension (especially from intravenous use), nausea • QT prolongation and torsades de pointes due to accumulation of active *N*-acetyl metabolite • Lupus-like syndrome (25%–50% with chronic use), especially in genetic slow acetylators • Oral drug no longer widely available
Quinidine	• Chronic treatment to prevent AF, VT, and VF	• Diarrhea (30%–50% of patients); diarrhea-induced hypokalemia may potentiate torsades de pointes • Marked QT prolongation and high risk (~1%–5%) of torsades de pointes at therapeutic or subtherapeutic concentrations • Immune thrombocytopenia (~1%) • Cinchonism: tinnitus, flushing, blurred vision, dizziness, diarrhea • Potent inhibitor of *CYP2D6* and *ABCB1*: altered effects of digitalis, many antidepressants, and others
Disopyramide	• Chronic treatment to prevent AF, VT, and VF	• Anticholinergic effects (dry eyes, urinary retention, constipation) • Long QT (torsades de pointes) • Depression of contractility can precipitate or worsen heart failure; paradoxically, this can be useful in hypertrophic cardiomyopathy to reduce outflow tract obstruction
Class IB: Na^+ Channel Blockers • Fast off rate • Little effect on ECG		
Lidocaine	• Acute treatment of VT and VF	• CNS: seizures and tinnitus • CNS: tremor, hallucinations, drowsiness, coma
Mexiletine	• Chronic treatment to prevent VT and VF	• Tremor and nausea
Class IC: Na^+ Channel Blockers • Slow off rate • Prolong PR and broaden QRS intervals		
Flecainide	• Chronic treatment to prevent PSVT, AF, VT, and VF in the absence of structural heart disease • Available in some countries for intravenous use in PSVT, AF • Useful in CPVT uncontrolled by β-blockers	• Much better tolerated than class IA or IB agents • Risk of severe proarrhythmia in patients with structural heart disease; increased mortality in patients with myocardial infarction (CAST) • Blurred vision • Can worsen heart failure

Class IC: Na^+ Channel Blockers • Slow off rate • Prolong PR and broaden QRS intervals (continued)		
Propafenone	• Chronic treatment to prevent PSVT, AF, VT, and VF in the absence of structural heart disease • Available in some countries for intravenous use in PSVT, AF • Alternative to flecainide for CPVT	• Also has β adrenergic blocking effects (worsening of heart failure and bronchospasm), especially prominent in *CYP2D6* poor metabolizers • Risk of severe proarrhythmia in patients with structural heart disease
Class II: β Blockers		
Nadolol Propranolol Metoprolol Many others	• Chronic treatment to prevent arrhythmias in congenital LQTS and CPVT • Rate control in AF • Widely used for other indications (angina, hypertension, migraine, etc.)	• β Adrenergic blocking effects (worsening of heart failure, bradycardia, bronchospasm) • Nadolol preferred by many for LQTS and CPVT
Esmolol	• Acute treatment to control rate in AF	• Ultrashort $t_{1/2}$, intravenous use only
Class III: K^+ Channel Blocker • Increase refractory period (prolong QT)		
Amiodarone	• Drug of choice for acute treatment of VT and VF and to slow ventricular rate and convert AF • Chronic treatment to prevent AF, VT, and VF	• Hypotension, depressed ventricular function and torsades de pointes (*rare*) with intravenous administration • Pulmonary fibrosis with chronic therapy, which can be fatal (requires periodic monitoring of lung function) • Many other adverse effects: corneal microdeposits, hepatotoxicity, neuropathies, photosensitivity, thyroid dysfunction • Note: tissue half-life of several months • Inhibitor of many drug-metabolizing and transport systems, with high potential for drug interactions
Dronedarone	• Chronic treatment to prevent AF	• Amiodarone analogue with lower efficacy than amiodarone • GI disturbances, risk for fatal hepatotoxicity • Increases mortality in patients with severe heart failure
Sotalol	• Chronic treatment to prevent AF, VT, and VF	• Also has β adrenergic blocking effects • High risk (~1%–5%) of torsades de pointes
Dofetilide	• Chronic treatment to prevent AF	• Few adverse effects except high risk (~1%–5%) of torsades de pointes
Ibutilide	• Acute treatment to convert AF	• High risk (~1%–5%) of torsades de pointes
Class IV: Ca^{2+} Channel Blockers • Nondihydropyridine • Inhibit SA and AV nodes • Prolong PR		
Diltiazem, Verapamil	• Acute intravenous use to convert PSVT and for rate control in AF • Chronic treatment to prevent PSVT and control rate in AF	• Hypotension (intravenous) • Sinus bradycardia or AV block especially in combination with β-blockers • Constipation • Worsening of heart failure
Antiarrhythmic Drugs With Miscellaneous Mechanisms		
Adenosine (activates A receptors)	Drug of choice for acute treatment PSVT	• Short $t_{1/2}$ (<5 sec) • Transient asystole • Transient dyspnea • Transient atrial fibrillation (rare)
$MgSO_4$	• Acute treatment of torsades de pointes	
Digoxin (Na^+-K^+–ATPase inhibitor)	• Ventricular rate control in atrial fibrillation • Modest positive inotropic effect	• Adverse effects common and include GI symptoms, visual/cognitive dysfunction, and arrhythmias, typically supraventricular arrhythmias with heart block or atrial or ventricular extrasystoles • Severe toxicities (e.g., with overdose) can be treated with antibody • Probably mortality neutral

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