A consideration of antiarrhythmic therapy

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THE PURPOSE of this article is to place into perspective newer avenues of antiarrhythmic therapy, including drugs and nonpharmacologic approaches.

Antiarrhythmic drugs

Types. A variety of antiarrhythmic drugs are available, both conventional and investigational. They can be divided into groups: those that exert blocking actions predominantly on sodium, potassium, or calcium channels, and those that block \( \beta \)-adrenergic receptors. Excessive subclassification of these drugs does not seem to be useful, primarily because it does not help in choosing effective drug therapy for a given patient. The classifications are also limited because they are based on the electrophysiologic effects exerted by an arbitrary concentration of the drug, generally on normal Purkinje fibers, often not even in arrhythmic preparations. The effects of these drugs depend on tissue type, species, the degree of acute or chronic damage, heart rate, membrane potential, the ionic composition of the extracellular milieu, and other factors. Thus, for example, lidocaine exerts little effect on a normal Purkinje fiber action potential upstroke at a pacing cycle length of 1000 msec but can profoundly depress it when the cell becomes depolarized and discharges at a rapid rate, such as might occur during ischemia-induced tachycardia. Many drugs exhibit actions that belong in multiple categories or operate indirectly, such as by altering hemodynamics, myocardial metabolism, or autonomic transmission. Some drugs have active metabolites that exert effects different from the parent compound. Not all drugs in the same class have identical effects, while some drugs in different classes have similar actions.

Supraventricular tachycardia

Choice of drugs for supraventricular tachycardias

General. Antiarrhythmic therapy, like antibiotic therapy, must be individualized, but unlike choosing a specific antimicrobial drug by testing its efficacy against the specific offending organism cultured from the patient, the appropriate and selective antiarrhythmic agent must be determined empirically. The need for such empiricism in treating many patients with supraventricular tachycardias such as atrioventricular nodal (AVN) reentry and tachycardias associated with an accessory pathway (AV reentry) has been modified dramatically over the past decade or more, in part because of results from invasive electrophysiologic studies that test the patient's response to a drug (table 1). These studies have made it possible to deduce the pathways involved in the presumed reentrant mechanism and to determine their electrophysiologic properties. The effects on these pathways of drugs with known and different mechanisms of action have been determined and these drugs can be anticipated to exert predictable effects because the pathways respond, for the most part, in a predictably normal electrophysiologic manner. This predictability is a key factor in choosing therapy. Moreover, when a drug terminates AV or AVN reentry, the mechanism by which this has occurred, e.g., the production of block in one of the reentry pathways, can be elucidated. Since the mechanism responsible for initiating and maintaining the tachycardia is often fairly constant from one episode to another, predictable responses to long-term therapy can be anticipated. Also, the electrophysiologic information obtained from invasive studies has permitted more accurate diagnosis of the supraventricular tachycardia by scalar electrocardiography and that information, coupled with data on predictable drug actions, permit drug selection that can be anticipated to exert a high degree of efficacy.

Thus, for example, in a patient with the usual AV reentry (presumptively diagnosed electrocardiographically by a delta wave during sinus rhythm and regular tachycardia with a normal QRS complex at about
TABLE 1
Tachyarrhythmias

<table>
<thead>
<tr>
<th>Pathways elucidated</th>
<th>Supraventricular(^a)</th>
<th>Ventricular</th>
</tr>
</thead>
<tbody>
<tr>
<td>EP properties</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>normal pathway</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Mechanism of tachyarrhythmia</td>
<td>Usually</td>
<td>Sometimes</td>
</tr>
<tr>
<td>Accurate therapeutic decision</td>
<td>Often</td>
<td>Seldom</td>
</tr>
</tbody>
</table>

\(^a\)AVN reentry or reentry associated with an accessory pathway.

200/min with a retrograde P wave in the ST segment), the reentrant loop can be surmised with a high degree of probability and specific drugs can be selected to exert a major depressant effect on the slow calcium channel-dependent AVN tissue used for anterograde conduction while other drugs can be chosen to affect the fast sodium channel-dependent tissue of the usual AV accessory pathway used retrogradely. The pathways in AVN reentry can be deduced in a similar fashion. The major unknown is whether the quantitative effects, not the qualitative effects, are appropriate to abolish the reentry loop or slow the ventricular rate if atrial fibrillation results. Founded firmly on the knowledge derived from these invasive electrophysiologic and electropharmacologic studies, a more focused therapeutic plan with a high likelihood of success can be outlined for most patients with these tachycardias. In essence, a tight-fitting match can be created between the mechanism of the tachycardia and the prescribed therapy. Given these considerations, what are the available choices?

Immediate termination. For the immediate termination of AV and AVN reentry, after simple vagal maneuvers have been tried, intravenous verapamil is the drug of choice because of its ability to slow conduction and prolong refractoriness in the AV node. Should atrial fibrillation supervene in the patient with the Wolff-Parkinson-White syndrome, the ventricular response over the accessory pathway may increase after intravenous (generally not after oral) verapamil. In that situation or for the patient presenting initially with atrial fibrillation and conduction over an accessory pathway, a drug that prolongs the refractory period of the accessory pathway (e.g., procainamide) should be used or application of electrical direct-current cardioversion considered, depending on the clinical situation. In some instances the drug that successfully terminates AV or AVN reentry can then be used for long-term oral therapy to prevent recurrences, considering the response to the acute episode akin to an electrophysiologic evaluation.

Long-term oral therapy. For long-term oral therapy to prevent recurrences of AV or AVN reentry, drugs that affect the AV node, such as digitalis, \(\beta\)-adrenergic-receptor blockers, or slow-channel blockers like verapamil or diltiazem, can be tried alone or in combination with drugs such as procainamide, quinidine, or disopyramide that affect the accessory pathway in AV reentry or the retrogradely conducting pathway in the usual variety of AVN reentry. Digitalis is contraindicated as single therapy in patients with Wolff-Parkinson-White syndrome and atrial fibrillation because it may increase the ventricular response.

Of the newer agents, amiodarone is particularly effective for patients with AV or AVN reentry. Although its side effects are many, for the most part they appear to be dose-related and, if lower doses are successful, as they seem to be for many patients with supraventricular tachycardias, side effects can be minimized. Amiodarone depresses conduction and prolongs refractoriness in both the AV node and accessory pathway, a particularly advantageous feature should atrial fibrillation occur. Encainide, flecainide, and propafenone, quite different from amiodarone with respect to electrophysiologic properties, similarly affect both the AV node and the accessory pathway to suppress both AV and AVN reentry and to decrease the ventricular response during atrial fibrillation. In general, side effects with these latter three drugs are quite tolerable, so it is logical to try therapy with them before amiodarone.

Thus, amiodarone, flecainide, encacline, or propafenone, alone or in combination with drugs that affect the AV node, would be the drugs of choice from the selection of newer agents to treat AV or AVN reentry that recurs despite treatment with conventional drugs. Efficacy is probably distributed fairly evenly among them.

In some patients who are dependent hemodynamically on atrial systole, such as those with hypertrophic cardiomyopathy, recurrent atrial flutter, or fibrillation can be a very troublesome and symptomatic arrhythmia. We have found amiodarone to be very effective in these patients, infrequently restoring sinus rhythm if atrial flutter or atrial fibrillation is present, but maintaining it after electrical reversion in the majority of patients. Often very low doses, e.g., 200 mg/day or on alternate days, are sufficient and side effects are minimal in this dose range.

Sinus nodal reentry less frequently presents a clinical problem due in part to slower rates of tachycardia,
and probably should be treated initially with drugs that affect the sinus node, such as digitalis or β- and slow-channel blockers. For other atrial tachycardias, slowing the ventricular response is often the therapeutic endpoint and the choice of drug or drugs that will be used to suppress the tachycardia itself is made empirically.

Choice of nonpharmacologic therapy for supraventricular tachycardias. Electrical devices that automatically or when activated by the patient or physician deliver competitive stimuli to the atrium or (less commonly) to the ventricle may be useful in selected patients with AV and AVN reentry. Rapid atrial pacing, or stimuli timed to a portion of the cardiac cycle, terminate virtually 100% of these two types of tachycardia. However, because pharmacologic management is usually successful, such approaches generally are reserved for the patient with recurrent tachycardia despite multiple drug trials or who is intolerant of drug management. A potential problem with these devices is that competitive atrial pacing may initiate atrial flutter or atrial fibrillation that may, particularly in the patient with an anterogradely conducting accessory pathway with a short refractory period, precipitate very rapid ventricular rates. However, an electrical device for the carefully screened and evaluated patient with AV or AVN reentry, often combined with drugs, can be a very successful and acceptable form of therapy.

On occasion, pacemakers can be used to prevent the onset of a variety of supraventricular tachycardias by pacing at rapid rates, at normal rates when the onset of tachycardia is related to bradycardia, or at short AV intervals to prevent retrograde invasion of an accessory pathway or reentry in the AV node.

Surgery to interrupt an accessory pathway should be considered for the patients with recurrent symptomatic tachycardia despite multiple drug trials, those with life-threatening tachycardia such as atrial fibrillation precipitating ventricular fibrillation, or for those whose consignment at a young age to a lifetime of pill consumption is unacceptable. Surgery for atrial flutter, AVN reentry, and some unusual forms of supraventricular tachycardia is still in the investigational stage, as is electrical ablation with catheter-delivered energy. These are areas to watch closely for future developments.

Ventricular tachycardia and ventricular fibrillation

Choice of drugs for ventricular tachyarrhythmias

General. Selecting therapy for the patient with ventricular tachyarrhythmias cannot be approached as logically and predictably as can treatment for supraventricular tachycardia (table 1). Individual pathways involved in the tachycardia cannot be studied, for the most part because the area of reentry, if that is the responsible mechanism, occurs in a small portion of the ventricle, precluding accurate electrophysiologic assessment with relatively gross extracellular stimulating and recording techniques. The right ventricle, generally remote from the origin of the ventricular tachycardia, is often the site of recording and stimulating and cannot be expected to provide electrophysiologic data relevant to a reentry loop or an automatic focus originating in the left ventricle. Even if the left ventricle is explored, the electrophysiologic properties of the microreentrant pathways cannot be discerned with the present tools. However, data from a variety of studies suggest that, if these pathways could be studied electrophysiologically, they probably would be very complex, including both normal and diseased tissue. In some cells, propagation or automaticity may be dependent on slow-channel activity and in others, it may depend on the fast sodium channel. Because the damaged area is so complex, in sharp contrast to the predictable response in many patients with supraventricular tachycardias, its response to antiarrhythmic agents with mechanisms of action based on data obtained in vitro in normal tissues cannot be predicted accurately.

Damaged ventricular myocardial and Purkinje tissue generally depolarize when injured, at least initially, and probably cell groups with several levels of maximum diastolic membrane potential exist, influenced by the nature and degree of damage, healing, and interposed scar tissue matrixes. In addition, alterations of the autonomic nervous system, heterogeneous blood flow patterns creating heterogeneous tissue concentrations of drugs, modulation of drug effects by active and inactive channel states, diastolic membrane potential and heart rate, varying drug kinetics due to genetic and other factors that influence the serum concentration of the parent compound and active metabolites, hemodynamic events, and other confounding variables may affect the cellular response to the drug and consequently the drug’s efficacy or toxicity. Although a predictable drug response can be anticipated in a few patients with unique types of ventricular tachycardia, it is not surprising that a focused therapeutic attack with a predictably high degree of success is difficult to anticipate for a specific patient with a ventricular tachyarrhythmia. Even the ideal end point with which to judge the therapeutic response, such as the suppression of spontaneous ventricular ectopic activity or response to programmed electrical stimulation, still has not been unquestionably determined.
**Mechanisms.** Most times we do not know why a drug terminates or prevents recurrence of a ventricular arrhythmia. Measurements of parameters such as refractoriness, excitability, and conduction are very useful in the characterization of the drug, but may not necessarily relate to the mechanism by which the drug is antiarrhythmic. Experimental studies usually establish the properties of antiarrhythmic agents rather than their antiarrhythmic properties. For example, a drug like amiodarone may suppress arrhythmias by exerting direct electrophysiologic actions on ventricular muscle and specialized conducting tissue that include prolongation of refractoriness and slowing of conduction velocity, or may act indirectly by slowing the heart rate, reducing ischemia, improving myocardial blood flow, or blocking α- or β-adrenergic receptors or the conversion of T₄ to T₃, reducing platelet adhesiveness or other factors. Very probably, in a general sense, antiarrhythmic drugs “isolate” the arrhythmogenic area by selectively making “sick cells sicker” and in some way uncoupling them electrically from the rest of the ventricle. It would not be at all surprising to find in damaged ventricles islands of “arrhythmic activity” that do not propagate to neighboring myocardium and thus do not produce clinically evident/manifest arrhythmias.

In contrast to many supraventricular tachycardias, it is seldom feasible to deduce the mechanism of a clinically occurring ventricular tachycardia from its response to a drug, given our present state of knowledge. Most drug actions are too nonspecific. For example, suppression of a ventricular tachycardia by verapamil may lead to the conclusion that the slow calcium current plays an important role in the mechanism of the tachycardia. However, the clinically used drug is a racemic mixture of two isomers, one of which exerts a slight but definite effect on the fast sodium channel. Also, among several other actions that may affect the arrhythmia, verapamil influences myocardial blood flow and produces reflex sympathetic stimulation while also producing α-blockade, all factors that could alter arrhythmogenicity independently from slow-channel suppression. Conversely, if lidocaine terminates an arrhythmia, it may be concluded that the slow inward current played no important role in the arrhythmia mechanism. However, lidocaine could eliminate an arrhythmia originating in a calcium channel-dependent automatic focus by blocking conduction in fast sodium channel–dependent tissue exiting from the focus rather than by actually suppressing the slow calcium channel–dependent automatic focus. The clinical result still would be suppression of the tachycardia. Indeed, except for reciprocating tachycardias associated with an accessory pathway in patients with the Wolff-Parkinson-White syndrome, for which virtually all evidence supports a reentrant mechanism, the electrophysiologic mechanisms responsible for other tachycardias remain speculative and there exist no pharmacologic, electrical, or surgical approaches so specific as to establish unquestionably the responsible electrophysiologic mechanism.

**Variability.** These factors make rational antiarrhythmic choices difficult for treating ventricular tachyarrhythmias. Also, in contrast to the fairly consistently recurring mechanisms in supraventricular tachycardias, the electrophysiologic mechanisms responsible for ventricular tachyarrhythmias may vary. For example, in the same patient, ventricular tachycardia may result from stable prior anatomic injury, e.g., ventricular scar or aneurysm, from acute myocardial ischemia, or from reperfusion that terminates acute ischemia. Each of these three causes may occur in the same patient, and probably will have unique electrophysiologic mechanisms and react differently to the same antiarrhythmic drugs. Ventricular fibrillation may respond to the same antiarrhythmic agent in still another fashion. Altered disease states may add to intrapatient variability of response. Thus, the anatomic-electrophysiologic status of a patient 2 weeks after a myocardial infarction probably is not the same as it is 6 months later. Therefore, it may be unreasonable to think that any single antiarrhythmic drug, e.g., quinidine, will be uniformly effective in reducing the incidence of sudden death in large numbers of patients in groups that are considered to be homogeneous but that actually are heterogeneous, such as patients who have had a myocardial infarction. The marked variability between patients, and potentially in the same patient, precludes determination of a consistent response to a single drug, and its seems unrealistic to rely on the effectiveness of one agent to suppress all the possible arrhythmogenic mechanisms in a given patient.

**Ideal drug.** We do not now have, and it is not likely that we will have in the near future, that elusive Holy Grail of antiarrhythmic therapy: the single antiarrhythmic agent with minimal side effects and ideal kinetics that is uniformly and predictably effective in preventing recurrence of ventricular tachyarrhythmia in a large percentage of patients with life-threatening arrhythmias. Unless an arrhythmia results from a common cause, e.g., ischemia, that can be prevented uniformly and in a predictable fashion with a closely related group of drugs like β-adrenergic–receptor blockers, it is not likely that one drug will be effective “across the board.” Each of the new (and old) drugs...
successfully suppresses electrically induced arrhythmias in approximately the same percentage of patients (about 20% to 30% of those referred for treatment of drug-resistant ventricular arrhythmias). Drugs suppress a higher percentage of spontaneously occurring ventricular arrhythmias. While one drug may be effective in one patient and not in another, it is not certain that any one of them is clearly more efficacious overall than the others. Amiodarone may be an exception. However, since only one drug chosen from a wide selection may be effective in a given patient, and since the drugs produce different side effects and patient tolerance differs, the availability of a wide variety from which to choose may be justified.

Comparison. It should be stressed that for several reasons it is very difficult to compare antiarrhythmic drug efficacy quantitatively, i.e., drug A is superior to drug B because it is effective in 25% more patients or more arrhythmias. Studies in patients with serious and symptomatic recurrent ventricular tachyarrhythmias generally are flawed, most often because the serious nature of the tachyarrhythmia precludes the use of scientifically rigorous principles that require placebo-controlled, blinded, prospective, and randomized trials. In addition, varying therapeutic end points (e.g., suppression of ambient arrhythmia present on long-term electrocardiographic recordings vs response to programmed electrical stimulation [with varying protocols]), and varying populations of patients (e.g., treated groups “top heavy” with patients having class 4 congestive heart failure and sustained ventricular tachycardia vs groups laden with patients having nonsustained ventricular tachycardia and no structural heart disease) are two of the many problems making comparative assessments difficult. Accurate tabulation of the prevention of symptomatic recurrences of ventricular tachycardia and ventricular fibrillation is extremely difficult to obtain and most often control data based on past history, natural history, or comparison between responders and nonresponders is used. Such data have inherent inaccuracies, magnified by the variable recurrence rate of most arrhythmias. Finally, patients referred to a medical center for treatment, who generally comprise the study groups in most of the published articles, are a selected group that may not represent the usual patient population seen in clinical practice.

Immediate termination. Given this lengthy list of qualifications, what are the antiarrhythmic drug choices for patients with recurrent ventricular tachyarrhythmias not responsive to conventional antiarrhythmic drugs?

A variety of investigational drugs have been used intravenously for immediate termination of ventricular tachycardia. However, none of them show clear superiority over conventional choices, although some have been successful in selected patients after conventional drugs have failed. Therefore, after a trial of lidocaine, and then perhaps intravenous procainamide and/or bretylium, electrical cardioversion would be recommended. If the arrhythmia recurs despite use of these drugs, we would probably then use intravenous amiodarone. For the patient with hemodynamic deterioration, direct-current cardioversion/defibrillation is certainly indicated.

Long-term oral therapy. Because of the fairly equal distribution of efficacy among most of the drugs, and the inability to predict beforehand that a particular patient will respond to a particular drug, generally the side effect profiles of the drugs most influence the initial choice of long-term oral therapy, a fact that is indicative of the general state of antiarrhythmic drug selection. Therefore, despite the apparently greater efficacy of amiodarone, it is often selected after other investigational drugs have been tried. Initial choices include propafenone or flecaïnide, in no particular order. Perhaps mexiletine would be tried next. Insufficient data exist regarding ethmozine, encaïnide, cibenzoline bepridil, and sotalol to place them in reasonable categories of effectiveness as yet.

Drugs in combination may be effective and also permit the use of lower doses of each drug, which may reduce side effects. Although suggestions for specific combinations have been offered, e.g., use of drugs with different electrophysiologic actions, no combination has emerged that is clearly superior to others and we generally opt for an empirical approach not unlike that used for the selection of single agents. It should be remembered that the drugs chosen may be synergistic, antagonistic, or noninteractive. Drugs that have each achieved partial suppression of the arrhythmia may be combined. From a practical standpoint, when we reach the point at which multiple drug therapy should be considered, the patient often is receiving amiodarone as the last attempt at single-agent therapy, and rather than wait weeks or months for its elimination, other agents are added to the amiodarone regimen. It is probably a good rule to reduce doses of both drugs when combinations, particularly with amiodarone, are used.

The above recommendations are applicable to patients with recurrent symptomatic ventricular tachyarrhythmias. However, it is very important to remember that ventricular tachyarrhythmias probably result from diverse electrophysiologic mechanisms and these guidelines may not necessarily apply to arrhythmias resulting directly from ischemia, either at its onset or
termination. Since we have scanty clinical information about which ventricular arrhythmias result solely from an anatomic obstacle, e.g., ventricular scar or aneurysm, and which are related to an ischemic event, or a combination of the two, hard and fast rules cannot be advanced. Experimental animal data, however, suggest that arrhythmias related to the onset or termination of ischemia are better treated by anti-ischemic and antisymptomatic approaches than with local anesthetic-type drugs. In this regard, the only agents demonstrated to reduce mortality after myocardial infarction are β-adrenergic-receptor blockers, not local anesthetics. Slow-channel blockers and local anesthetics are presently being evaluated in this postinfarction setting.

Choice of nonpharmacologic therapy for ventricular tachyarrhythmias

Surgery. Should drug therapy prove ineffective or not well tolerated, surgery7, 8 or electrical devices9, 10 may be considered alone or in combination. The surgical candidate generally is a patient who has recurrent life-threatening ventricular tachycardia that can be mapped preoperatively and/or intraoperatively, a reasonably localized ventricular lesion such as an aneurysm, and sufficient myocardial reserve to withstand the stress of surgery. Coronary bypass surgery alone may be indicated only if ischemia is definitely established as the cause of the arrhythmia. Therapy with an electrical device can be combined with surgery in that leads for an implantable cardioverter/defibrillator can be sewn in place at the time of ablative surgery. Determination of the antiarrhythmic efficacy of electrical and chemical ablation techniques awaits documentation from further experience.

Electrical devices. An implantable cardioverter-defibrillator9, 10 may be considered for the patient who has recurrent life-threatening ventricular tachyarrhythmia and may not be a surgical candidate because he cannot tolerate the surgery or has ventricular tachyarrhythmia that cannot be mapped or resected or progresses rapidly to ventricular fibrillation. One advantage of electrical cardioversion or defibrillation is that it successfully terminates the ventricular tachyarrhythmia in a very high percentage of patients with life-threatening ventricular arrhythmias independent of the cause of the heart disease, heart rate changes, hemodynamic status, levels of autonomic tone, pharmacokinetic influences, and all of the other variables mentioned earlier. In 1980 Mirowski et al.9 demonstrated the usefulness of an implantable device in patients with ventricular fibrillation, and more recently we10 presented data on an implantable pacemaker-cardioverter for patients with ventricular tachycardia. Next-generation devices of this type will be capable of delivering competitive pacing stimuli, synchronous cardioversion, or defibrillation shocks automatically in a programmable, escalating fashion, depending on the spontaneous cardiac rhythm. They also may have recording capabilities so that a record of the rhythm disturbance and device performance may be obtained.

Such electrical therapy has the drawback of not preventing a tachyarrhythmia from occurring, even though it promptly terminates it after the onset. Although efforts to use electrical therapy to prevent arrhythmias are being explored, in reality such anti-tachycardia devices probably will be used in conjunction with antiarrhythmic drug therapy to decrease recurrence of arrhythmias and minimize the number of times a patient may need to be shocked electrically. Having an implantable pacemaker-cardioverter-defibrillator available may permit some leeway in drug selection in the event that the drug fails to prevent recurrence of arrhythmia or is arrhythmogenic. One can envision giving a drug in lower doses that are well tolerated to prevent nine of 10 episodes of ventricular fibrillation, with the device terminating what would have been the tenth episode. In addition, such devices could permit, for the first time, the ethical study of control or placebo-treated groups of patients who have had recurrent ventricular tachycardia or ventricular fibrillation in order to evaluate drug efficacy according to more scientifically acceptable methods. Recording capabilities will document accurately the rhythm disturbance to provide proof of the arrhythmic event.

At present, the use of such devices is restricted, appropriately, to limited patient populations. Further progress in accurate and reliable identification of tachycardias is required before recommending a more widespread application of such electrical approaches. Although more expensive than ordinary pacemakers, these devices probably will become cost-effective by enabling rapid patient discharge from the hospital and reducing the need for frequent readmission of patients with recurrent ventricular tachycardia and fibrillation. Electrophysiologic studies to test the efficacy of drugs and the electrical device can be performed noninvasively with the pacemaker-cardioverter in an outpatient setting.10 Most importantly, however, the defibrillator9 appears to reduce the incidence of sudden death in a heterogeneous population of patients with coronary artery disease, cardiomyopathy, long QT syndrome, and other problems. Reduction in defibrillation threshold may make possible transvenous implantation of defibrillators. As this mode of therapy
becomes perfected, with accurate identification of tachycardias and safe, effective administration of therapy, application may even reach the point of prophylactic implantation in high-risk populations before a potentially lethal arrhythmia occurs. Further investigation into the effects of drugs on the efficacy of these devices is necessary.

Selection of candidates for therapy

One must consider carefully which patients with ventricular arrhythmias should be treated, particularly in view of the proarrhythmic effects of these agents. Initially, attempts should be made to uncover easily treatable causes of arrhythmias, such as hypokalemia. No data exist to support treating patients with asymptomatic premature ventricular complexes (PVCs). Thus, suppression of spontaneous PVCs rather than suppression of recurrences of sustained or nonsustained ventricular tachycardia or ventricular fibrillation may not be relevant in defining a drug’s therapeutic potency. In fact, it is difficult to understand the recent infatuation with so-called PVC killers (a repugnant and very unscientific term) unless these drugs also suppress ventricular tachycardia and fibrillation. Suppression of PVCs and of ventricular tachycardia or fibrillation may have different “thresholds.” That is, different drugs or different concentrations of the same drug may suppress PVCs and not tachycardia or vice versa, possibly because the electrophysiologic mechanism responsible for the PVC may be different from that responsible for the ventricular tachycardia.11

We would consider for therapy those patients with structural heart disease who have asymptomatic or symptomatic sustained or nonsustained ventricular tachycardia and those without structural heart disease who have symptomatic sustained or nonsustained ventricular tachycardia. Patients resuscitated from ventricular fibrillation not associated with an acute myocardial infarction should also be treated. While convincing objective data to support this approach do not exist in all groups of patients, this seems to strike a reasonable balance between the risks of therapy and the risks of the arrhythmia. Close monitoring of the patient’s response is necessary to avoid drug-induced arrhythmogenic responses. Future studies may demonstrate that so-called idiosyncratic drug reactions may be explained by patients with genetically determined unusual metabolic pathways that result in production of arrhythmogenic metabolites.

Future considerations

There can be no doubt that in vitro and in vivo electrophysiologic studies in animals and humans have advanced our knowledge of the mechanisms of arrhythmogenesis and of drug action and that such studies must continue. However, advances in understanding actions of antiarrhythmic agents that have directly benefited the patient with ventricular arrhythmia have been slow and, except for producing a wider choice of drugs, we have progressed little clinically over the past 25 years. Most of these new drugs, however, are simply another iteration of existing drugs, with slightly different efficacy or side effect profiles. Progress must come from knowledge of the autonomic, metabolic, or cellular changes associated with the genesis of cardiac arrhythmias to provide insight into therapy that actually corrects basic defects rather than simply suppresses them. New diagnostic procedures such as the use of nuclear magnetic resonance, positron-emission tomography, NAD-NADH fluorescence, or voltage-sensitive dyes may not only provide insight into arrhythmogenic mechanisms, or at least the abnormal environment in which arrhythmias arise, but may help differentiate subpopulations of patients that may respond predictably to one or another antiarrhythmic drug. One can envision development of site-specific antiarrhythmic agents that could be directed to designated areas of the myocardium identified by such imaging techniques. While conventional invasive electrophysiologic studies are essential to categorize the usual electrophysiologic effects of a drug on specialized conducting tissue and muscle and may be useful in rapidly assessing drug efficacy, it is difficult to see how such studies, in their present form, will be able to provide further insight into mechanisms of drug action or deliver us from the need for empirical drug selection. Major criticisms of almost all of these studies involve their lack of adequate controls, small numbers of patients, and short-term follow-up.

In 1914, Wencebach noted empirically that two patients with paroxysmal atrial fibrillation who were treated prophylactically for malaria with an extract of cinchona bark (quinine) frequently reverted to sinus rhythm. While we have made enormous strides over the intervening 70 years, pharmacologic control of arrhythmia still remains predicated on an individual, patient-by-patient, pharmacologic experiment, determined by trial and error, and tempered by good clinical judgment, whether one uses criteria obtained from noninvasive or invasive studies.

References

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