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ANTIARRHYTHMIC DRUGS

Raymond L. Woosley

Department of Pharmacology, Georgetown University, Washington, DC 20007

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INTRODUCTION

Antiarrhythmic drugs are among medicine's most challenging to understand. Although research in recent years has improved our understanding of the cellular mechanisms of arrhythmias and of the actions of clinically effective drugs, the general approach to therapy remains empiric for most patients. Nevertheless, a multidisciplinary team approach has allowed arrhythmia centers to develop the expertise to increase diagnostic accuracy and therapeutic efficacy for patients with serious arrhythmias. These centers provide expertise in clinical cardiology, cardiovascular pharmacology, invasive clinical electrophysiology, and electrical devices such as the implanted automatic cardioverter/defibrillator. Recent recognition of the potentially lethal side effects of antiarrhythmic drugs (1) has led to a reappraisal of their roles in therapy and the call for additional research into the pharmacology of drugs for the treatment of arrhythmias (2, 3). A broad review of the diagnosis and management of arrhythmias is beyond the scope of this review. The recent literature on acute and chronic therapy of arrhythmias should be consulted to appreciate the high degree of uncertainty and rapid evolution of knowledge in this area (4, 5).

The greatest impact on the therapy of arrhythmias in recent years has come from the early results of the Cardiac Arrhythmia Suppression Trial (CAST) that were announced by the National Institutes of Health and the Food and Drug Administration in early 1989 (1). When CAST was being planned there was ample evidence that the presence of asymptomatic ventricular arrhythmias is an independent risk factor identifying a subpopulation of patients with recent myocardial infarction at increased risk for mortality (6, 7). Likewise, new sodium channel blocking drugs, predominantly analogs of lidocaine or procainamide, had been found to be very effective in suppressing premature

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ventricular depolarizations (PVDs) and were being approved for marketing. A National Institutes of Health-sponsored study, the Cardiac Arrhythmia Pilot Study (CAPS), found encainide, flecainide, and moricizine able to suppress VPDs with a low and acceptable incidence of side effects (8). CAPS was not intended to have the power necessary to evaluate the effects of antiarrhythmic drugs on mortality but provided the first placebo-controlled comparison of drugs in a population with a recent myocardial infarction, valuable information for the planning of CAST. CAST was designed to mimic clinical practice and test the hypothesis that suppression of asymptomatic PVDs in a population with prior myocardial infarction would reduce the incidence of sudden arrhythmic death. Patients at moderate risk for sudden death, whose PVDs and/or nonsustained ventricular tachycardia (VT) could be suppressed by encainide, flecanide, or moricizine, were randomly assigned to remain on therapy with the effective agent or be switched to an identical placebo. The study was planning to enroll 4400 patients over a three-year period and follow them for two to five years. CAST was interrupted temporarily in March, 1989, when it became clear that two of the drugs, encainide and flecainide, were causing a 2–3-fold increase in mortality compared to that in patients whose arrhythmias had been previously suppressed but randomized to receive placebo (See Figure 1). CAST-II continues and compares moricizine and placebo with slight modifications to the protocol. However, the original

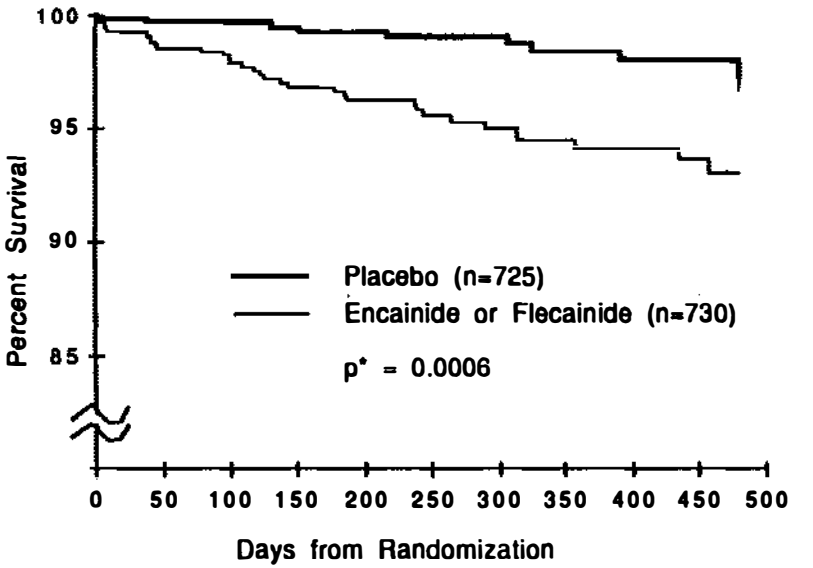

Figure 1 Survival among 1455 patients randomly assigned to receive encainide, flecainide (n=730; *thin line*), or matching placebo (n=725; *thick line*). The cause of death was arrhythmia or cardiac arrest (p=0.0006). (Reprinted with permission from ref. 1.)

hypothesis has been tested and it is clear, at least with these two drugs, that suppression of asymptomatic PVDs does not decrease mortality. Whether this only pertains to these drugs will depend on the results of CAST-II. If moricizine fails to decrease mortality, it is unlikely that other drugs in this class will ever be tested in this population for their effects on mortality.

Local anesthetic antiarrhythmic drugs are generally assumed to be effective in a proportion of patients with life-threatening or highly symptomatic arrhythmias (9). However, for ethical reasons, they have never been formally evaluated in placebo-controlled trials. Efficacy and tolerance are highly variable and depend on the drug being considered, the arrhythmia being treated and other factors such as ventricular function. Table 1 provides an overview of the relative efficacy and tolerability of these drugs in various types of arrhythmias. This table is based on the author's personal experience and review of the literature. Because there have been few direct comparisons of drugs, this is a highly subjective comparison but generally agrees with most other similar evaluations (9, 10).

The overall impressions apparent from such comparisons are: (*a*) No single agent has uniform efficacy or safety; (*b*) Amiodarone has a high degree of efficacy in a broad spectrum of arrhythmias but its use is limited by serious toxicity; (*c*) Agents with predominantly Class I action have modest efficacy in

Table 1 Relative efficacy of antiarrhythmic drugs

Drug	SVT/AF	PSVT	WPW	MI/PVDs	Chronic VPDs	VT/CA	Mortality
Quinidine	++	++	++	++	++	+	↑ ↓
Procainamide	+	+	++	++	++	++	ND
Lidocaine	−	−	−	+++	+	+	ND
Disopyramide	+	+	++	+	++	+	ND
Tocainide	−	−	−	+	++	+	ND
Mexiletine	−	−	−	+	++	+	↑ ↓
Flecainide	++	−?	+++	ND	++++	++	↑
Encainide	+	−?	+++	ND	++++	++	↑
Propafenone	++	+	+++	ND	++++	++	ND
Moricizine	ND	ND	ND	++	++	+	Pending
Amiodarone	++	++	++	++	++	+++	Pending
Bretylium	ND	ND	ND	+	++	+++	ND
Sotalol	++	?	?	++	++	+++	↓
Verapamil	+	+++	?	−	−	−	↑ ↓
Diltiazem	+	+++	?	−	−	ND	−

ND = not determined; + = minimally effective; ++++ = highly effective but not uniformly; ? = case reports indicate possible efficacy; − = no effect; ↓ = decrease; ↓ ↑ = conflicting preliminary reports. SVT = supraventricular tachycardia; AF = atrial fibrillation; PSVT = paroxysmal supraventricular tachycardia; WPW = Wolfe-Parkinson-White syndrome; MI/PVD = premature ventricular depolarizations after myocardial infarction; VT/CA = ventricular tachycardia and/or cardiac arrest; Mortality = evidence available that the drug has an effect on mortality, ↑ indicates an increase in mortality and ↓ indicates a decrease in mortality due to the drug.

serious arrhythmias; (*d*) Agents with potent sodium channel blocking activity are potent suppressors of PVDs but quinidine (11) and the two most effective agents, encainide and flecainide, actually increase mortality (1); (*c*) Agents with predominantly calcium channel blocking activity have proven efficacy in the treatment of AV nodal re-entrant arrhythmias and lack efficacy for most ventricular arrhythmias.

ROLE AND VALUE OF CURRENT CLASSIFICATION SYSTEMS

Vaughan Williams and Other Classifications

Because the treatment of arrhythmias has proven to be so difficult, physicians and investigators have sought an organizational framework that would allow them to better contrast and understand the drug actions that might be antiarrhythmic. One of the first attempts was that by Vaughan Williams shown in Table 2 in which drugs were placed in classes based on their predominant antiarrhythmic action (12). In recent years, a subclassification of drugs with Class I action has been proposed based on differences in their potency and their differential effects on repolarization (13). Subclass IA drugs have moderate potency at blocking the sodium channel and also prolong repolarization. Subclass IB agents have the lowest potency as sodium channel blocking action and produce little if any change in action potential duration. Subclass IC are the most potent sodium channel blocking agents and have only limited effects on repolarization.

An important aspect of this and all classification schemes was emphasized in a more recent editorial by Vaughan Williams (14) in which he noted that the approach that bears his name was intended to be a classification of

Table 2 Vaughan Williams classification of antiarrhythmic actions of drugs

Class	Action	Prototypes
I	Sodium channel blockade	Lidocaine Procainamide
II	Antagonism of sympathetic nervous system	Propranolol
III	Increased refractoriness	Amiodarone Bretylium
IV	Calcium channel blockade	Verapamil Nifedipine
V	Chloride channel blockade	Alinidine

Table 3 Associated adverse cardiac effects

Class I	Class II	Class III	Class IV	Class V
Proarrhythmic effect	Sinus bradycardia	Sinus bradycardia	Atrioventricular block	Sinus bradycardia
Negative inotropic effect (dose-dependent)	Atrioventricular block	Torsades de pointes	Negative inotropic action	
Infranodal conduction block	Depression of LV function (if adrenergic-dependent)			
IA—Torsades de pointes				

Table 4 Antiarrhythmic actions

Drugs	Class I	Class II	Class III	Class IV	Other actions
Quinidine	++		++		α blockade
Procainamide	++		+		Ganglionic blockade
Lidocaine	+				
Disopyramide	++		+*		Anticholinergic
Tocainide	+				
Mexiletine	+				
Flecainide	+++			+	K^+ channel blockade
Encainide	+++				
Propafenone	+++	+**			
Bretylium			++		Sympathomimetic and sympatholytic
Amiodarone	++	++	++	+	α receptor blockade, muscarinic block
Sotalol		++	+++		
Verapamil	+			++++	
Diltiazem				+++	

* stereospecific effects
** influenced by metabolic phenotype

antiarrhythmic "actions", not of "drugs". This is not simply a semantic point but one that deserves careful consideration. Physicians might mistakenly conclude that the drugs within a class are clinically similar and that if patients fail to respond to a drug in a given class, they should not respond to the others in that class. Clinical studies have found that such predictions are unreliable and that patients have approximately an equal chance of responding to any agent, independent of their response to other drugs of that class (8). The only partial exception to this is the greater, but not complete, concordance that has been seen with response to the congeners of lidocaine (15, 16). The lack of predictive accuracy within a class is readily understood when one realizes that few of the drugs have only a single action and that the metabolites of the drugs often have actions different from the parent (17, 18). A classification system such as the one proposed by Vaughan Williams finds its greatest utility as a conversational shorthand and for its ability to explain adverse effects such as those listed in Table 3, that are extensions of a drug's pharmacologic action.

Limitations on Current Classifications

The most important limitation to current schema is the fact that almost all of the currently available drugs have multiple actions. Table 4 lists the drugs and their actions. It is rarely if ever apparent which of these actions are responsible for suppression of an arrhythmia for a given patient. This is especially

true with amiodarone since any of its multiple actions may contribute to its high degree of efficacy (19–22).

Studies of the metabolites of antiarrhythmic drugs have made it clear that the metabolites contribute to or are primarily responsible for the antiarrhythmic actions of some drugs (e.g. encainide). The best example of this is procainamide and its major metabolite, N-acetylprocainamide. N-acetylprocainamide is the product of N-acetyl transferase, a hepatic enzyme that has a bimodal distribution of the populations that have been studied (23). In the United States, fifty-five percent of the caucasian or black populations have the rapid acetylator phenotype and, during steady-state therapy with procainamide, actually have greater concentrations of N-acetylprocainamide in plasma than procainamide (24). Whereas procainamide has moderate potency as a Class I sodium channel blocking drug, N-acetylprocainamide has only Class III action (prolongs repolarization) (17). This explains the observation that patients whose arrhythmias respond to intravenous procainamide (before any N-acetylprocainamide accumulates) may fail to respond to oral therapy with N-acetylprocainamide and vice versa (25).

Encainide is another example of an antiarrhythmic agent that has metabolites with different actions. Encainide also has polymorphic metabolism but in this case, it is oxidized by the $P450_{IID6}$ responsible for the metabolism of debrisoquine and many other drugs including metoprolol, flecainide, and propafenone (26). Extensive metabolizers of encainide have concentrations of 3-methoxy-O-desmethylencainide (MODE) in plasma that are in the range found to be active when the metabolite is given to patients with arrhythmias (27). However, poor metabolizers (PM), 7–9% of the US population, do not have detectable levels of MODE in plasma (28). Electrophysiologic studies in animals and clinical studies have found that MODE and encainide have very different actions. In addition to blocking sodium channels, MODE prolongs the QT interval and refractoriness (a Class III action) at concentrations that are antiarrhythmic in patients (18). In contrast, encainide has only sodium channel blocking activity and QT interval prolongation is not seen when encainide is the sole active agent, i.e. in the PM phoenotype (29, 30). Therefore, a patient's metabolic phenotype is a determinant of the types of antiarrhythmic action that can be acting to suppress an arrhythmia.

There are other examples in which the classification system may be misleading. Subjects with the poor metabolizer phenotype for propafenone (an agent with Class IC action) have more beta receptor antagonism (Class II action) than extensive metabolizers (31). Although disopyramide is placed in Class IA, one stereoisomer prolongs repolarization and another shortens repolarization (32). The predominant effect depends on the degree of stereospecificity exhibited in their elimination (33). For quinidine, far

greater effects on repolarization are seen during oral therapy than after an acute intravenous infusion (34).

In summary, the actions of drugs that might be antiarrhythmic for patients are only poorly predicted by the Vaughan Williams classification system. They can be better anticipated by a full understanding of the multiple actions of the drugs and their metabolites combined with knowledge of their clinical pharmacology so that one might predict the factors influencing drug action.

Future Approaches

In the past decade, pharmacologists have gained a better understanding of the actions of antiarrhythmic drugs. It is now generally accepted that the sodium channel blocking drugs have major differences in their affinity for or access to the receptor that regulates the influx of sodium. Differences in affinity or access to the sodium channel lead to differences in the time constants for onset or decay of sodium channel blockade (35–37). As can be seen in Figure 2, this leads to different profiles for onset of block and has been proposed by Campbell as a basis for subclassifying drugs (38). Similar concepts are evolving for the blockade of other channels, e.g. the potassium and calcium channels (39, 40).

One potential flaw of any system based on blockade of "normal" ion channels is that it may not appropriately describe the actions of drugs on the cause of an arrhythmia or the substrate that sustains an arrhythmia. Although many have proposed arrhythmia mechanisms, such as "re-entry", "abnormal

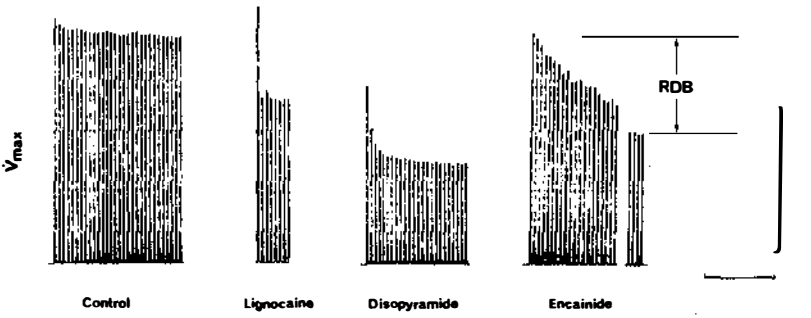

Figure 2 The effect on maximum velocity of phase O ($\dot{V}_{max}$) of a train of action potentials in previously quiescent tissues in control solution and in the presence of lidocaine (2×10^{-8} mol/l), disopyramide (1-^{-4} mol/l) and encainide (3×10^{-6} mol/l). The interstimulus interval in each case is 300ms. The spikes represent the $\dot{V}_{max}$ of successive action potentials. There is minor rate-dependent depression of $\dot{V}_{max}$ (RDB) in control solution and marked and approximately equal depression in the presence of each drug. RDB develops rapidly with lidocaine, slowly with encainide (only the first 20 and last 4 beats of a 60 beat train are shown) and at an intermediate rate with disopyramide. Vertical calibration: 200V/s; horizontal calibration: 5s. (Reprinted with permission from ref. 38.)

automaticity" or "boundary currents", these descriptive terms do not address the true biochemical mechanism initiating electrical abnormalities. Basic research into the biochemical changes within cells and the intercellular communications causing and/or sustaining arrhythmias is absolutely essential before more specific forms of therapies or useful classification systems can be designed.

MECHANISM OF ACTION OF CURRENT DRUGS

Modulated Receptor Theory for the Sodium Channel

The majority of drugs found effective in the treatment of cardiac arrhythmias are sodium channel blocking drugs. In high concentrations, they are also capable of blocking nerve conduction due to their local anesthetic actions. However, at the concentrations achieved in plasma with usual antiarrhythmic dosages, most drugs, other than IC drugs, have little discernible actions on the normal myocardial conduction system. The early observations that ischemic (depolarized) tissue or rapidly depolarizing tissue has greater sensitivity to sodium channel block by drugs such as lidocaine or quinidine, prompted a search for other potential models for the interaction of these drugs with the sodium channel (35–37). The enhancement of sodium channel blockade seen in rapidly depolarizing tissue has been termed "use-dependent sodium channel block" and is thought to be responsible for the efficacy of these drugs in slowing and converting a tachycardia with minimal effects on conduction in normal tissue stimulated at physiologic rates.

Hodgkin & Huxley theorized that the sodium channel of neural tissue cycles through three different states during the action potential (41). To explain use-dependent block, Hondeghem & Katzung (36) and Hille (35), in 1977, adapted this theory to cardiac tissue and proposed what is currently termed the "modulated receptor theory" (MRT). As shown in Figure 3, the sodium channel is theorized to cycle from rested (closed), to activated (open) and to an inactivated state. Under normal resting conditions, the membrane is hyperpolarized and the sodium channels are predominantly in the rested (R) state. During the upstroke of the action potential, the membrane becomes depolarized when most of the channels change to the activated open state (A) and sodium is allowed to rapidly cross the cell membrane. The sodium current (I_{Na}) rapidly decays as most of the channels move to the inactivated state (I). The MRT assumes that drugs bind preferentially to certain channel states and that channels bound to drug exhibit different transition rates between the different states than do unbound channels.

By conducting an analysis of the data from rigorous in vitro stimulation

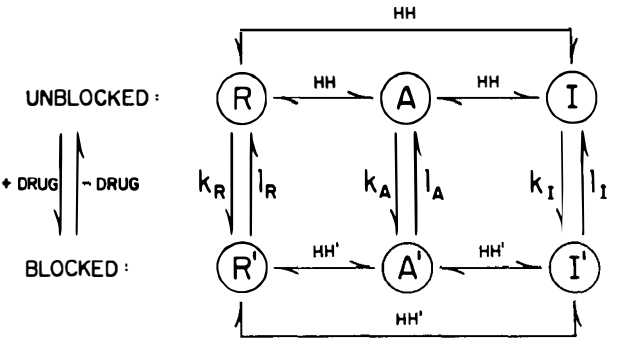

Figure 3 Diagram of modulated receptor mechanism of action of antiarrhythmic drugs. R = sodium channels in the rested state; A = sodium channels in the activated state; I = sodium channels in the inactivated state; R',A',I' = drug-associated states; HH = Standard Hodgkin-Huxley rate constants; HH' = same but voltage-dependence altered by drug binding; k_R, k_A, and k_I represent association rate constants; I_R, I_A, and I_I represent the dissociation rate constants for the respective fractions. (Reprinted with permission from ref. 14.)

protocols designed to examine the actions of drugs within the constructs of the MRT, the relative affinity of drugs for the different states of the sodium channel can be estimated. Drugs with high affinity for the rested state would be toxic and those with potential clinical utility would have affinity for the open and/or inactivated state. Table 5 lists the relative affinities of several drugs and the time constants for recovery from block that have been found.

Because lidocaine has a short time constant for onset and recovery from block, block occurs with the first depolarization and little additional block occurs with subsequent depolarizations. However, as shown in Figure 2, flecainide and similar drugs with longer time constants continue to accumulate block and require a longer time before reaching a steady-state level of block (42). Disopyramide and procainamide have an intermediate pattern and intermediate time constants. The following characteristics of these drugs can be explained by the MRT and have been reviewed by Katzung et al (43):

1. Selective depression of conduction in depolarized tissue;
2. Selective depression of automaticity in ectopic foci;
3. The selective effects of lidocaine and phenytoin on ventricular and Purkinje cells as compared to atrial cells;
4. Competitive interactions between certain sodium channel blockers;
5. Additive interactions between drugs that prolong action potential duration and those with high affinity for the inactivated channels.

Table 5 Affinity of selected drugs for sodium-channel receptors and time constants of recovery[1]

Drug	Relative affinity* for channel state			Recovery time constant† (sec)
	Rested	Open	Inactivated	
Amiodarone	1×10^{-3}	0.1	5.2	1.6
Aprindine	$.15 \times 10^{-3}$	3.4	26	3.0
Bupivacaine	50×10^{-3}	.0001	114	1.5
Lidocaine	$.04 \times 10^{-3}$	2	2.6	0.2
Procainamide	$.06 \times 10^{-3}$	.0027	.28	2.3
Quinidine	0	1.0	0	5.5

* Relative affinity calculated as the reciprocal dissociation constants referred to the K_d of quinidine for the open state (103 μM).
† Recovery of V_{max} at −85 mV.
[1] Adapted from ref. 111 with permission.

This last prediction of the MRT led Hondeghem to hypothesize that lidocaine and quinidine would have synergistic activity in blocking sodium channels (44). This prediction was verified in patients with ventricular arrhythmias by Duff et al (45). These investigators compared therapy with mexiletine (a lidocaine analog) and quinidine, alone and in combination, and found greater efficacy and fewer side effects when patients received lower dosages of the two drugs in combination. The additional efficacy of this combination is predicted by the MRT because prolongation of repolarization prolongs the inactivation phase of the sodium channel allowing more time for mexiletine (an inactivated state blocker) to produce its block. This combination has been evaluated in several animal or tissue models and has been found to be additive or in some cases synergistic (46, 47). More recent studies have continued to find the combination effective for resistant life-threatening ventricular arrhythmias (48).

Guarded Receptor Model

There are few major functional or clinically relevant differences between the MRT and the guarded receptor theory. Whereas the MRT uses a mathematical approach to calculate drug affinities to the three theoretical states of the channel, the GRT assumes that the affinity of a drug for the receptor is a constant. Instead, the GRT places diffusional constraints on the access and egress of drug between its binding site within the channel and its pools in the membrane and the cytoplasm (37). The GRT has been applied in the analysis of the in vitro characteristics of sodium channel blocking drugs as predictors of their antiarrhythmic and proarrhythmic actions (49). For example, QX-314, an analog of lidocaine that is positively charged, cannot penetrate

membranes and should only have access to the sodium channel receptor when the channel is open. Support for this is seen in the fact that when the drug is placed inside a single cell with a micro-pipette, it does not produce block until the channel is opened by depolarization (50). That is, even after prolonged intracellular exposure to the drug, no block occurs with the first depolarization. Additionally, the GRT provides a useful framework for understanding the ability of low pH to potentiate sodium channel blockade by ionizable drugs (51).

Other Models for the Sodium Channel

Figure 4 displays the current Hodgkin-Huxley concept of the interactions between the hypothetical m and h gates to determine the state of the sodium channel. Although the GRT and the MRT are based on different mechanisms of drugs interacting with the gates, they are still consistent with this anatomical model.

Other hypotheses have been proposed to explain the functional characteristics of the sodium channel and the actions of drugs. Courtney (52) has examined the molecular size and configuration of forty sodium channel blocking drugs and proposed the size/solubility hypothesis to account for the

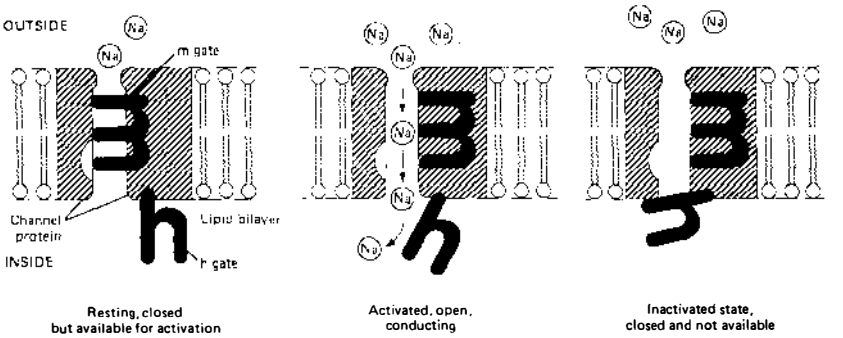

Figure 4 Schematic diagram of the cardiac sodium channel. The channel (shaded area) is a protein that spans the lipid bilayer membrane. In the resting state, fully polarized membrane (left), the h gate is open and the m gate is closed, preventing any movement of sodium ions through the channel. With an appropriate stimulus, the m gate opens, allowing rapid influx of sodium ions (middle). Approximately one msec later, the h gate closes, shutting off the sodium current (right). Additional stimuli applied to the inactivated channel cannot open it (the h gate is already closed); therefore, it is "unavailable." The actual shapes of the channel and the gates are unknown, and those shown are purely symbolic. The light area at the lower left end of the channel is a possible location for a local anesthetic receptor. (Reprinted with permission from ref. 122.)

excellent relationship he observed between recovery time constants and a factor termed "adjusted molecular weight". The adjusted molecular weight takes into account the drugs' molecular weight, pK, and lipid partition coefficient. This hypothesis states that smaller antiarrhythmic drugs with high lipid distribution capabilities provide more rapid recovery or repriming kinetics. This hypothesis is compatible with a model for the sodium channel as a cylindrical pore having a 4.1 Å radius.

Actions on Potassium Currents

Table 6 lists the several potassium currents that have been identified using in vitro intracellular recording techniques. Potassium currents, predominantly the delayed rectifier, I_k, flow during the repolarization phase of the action potential (AP). Block of the potassium current(s) during the plateau phase of the AP is considered to be the mechanism of many of the drugs that prolong the refractory period (53). Examples of these drugs are quinidine, sotalol N-acetylprocainamide, and amiodarone. Because of the perception that the high degree of clinical efficacy of amiodarone is due to its actions to prolong the AP and refractoriness, many new agents are being developed that have as their predominant action blockade of potassium channels (see below). However, one must be cautious in extrapolating the results from in vitro studies of the effects of drugs on ion channels to in vivo effects on action potential characteristics or refractoriness. Most drugs have effects on multiple channels and the effects are often voltage-, time-, concentration- and/or

Table 6 Potassium currents

Current	Symbol	References
Delayed rectifier	I_K	112, 113
Background (inward rectifier)	I_{KI}	114, 115
Transient outward	I_{to}	116
Ca^{++} activated	–	117
High conductance plateau	I_{Kp}	118
Acetylcholine activated	$I_{K,ACh}$	119
ATP activated	$I_{K,ATP}$	120

rate-dependent. However, in general, drugs that block the delayed rectifier potassium current can be expected to increase the duration of the action potential plateau and prolong the refractory period (53). Another generalization that can be made, but with less confidence, is that these drugs will have the propensity to cause a particular form of arrhythmia, torsades de pointes (54). Carlsson et al (55) found an excellent relationship between the potency of six antiarrhythmic drugs to prolong QT interval and their arrhythmogenic dose in a rabbit model of torsades de pointes. Nevertheless, some drugs such as amiodarone prolong the QT interval but have a very low incidence of torsades de pointes compared to quinidine (56).

Hondeghem & Snyders note that most of the available drugs that prolong repolarization have *negative* rate-dependence, i.e. the drugs have the greatest effect to prolong repolarization at slower rates. Figure 5, taken from the review by Hondeghem & Snyders, displays the negative use-dependence seen with the available drugs with Class III action. They point out that the ideal drug would have *positive* rate-dependence and produce its greatest effects on refractoriness at faster rates (see below). Such an action would tend to cause spontaneous conversion of a tachycardia and may be less likely to induce early afterdepolarizations (EADs) and torsades de pointes.

Two recent observations are relevant to these considerations. Flecainide, a drug generally felt to be prototypic of Subclass IC, was found to block the delayed rectifier potassium current (57) and to have positive use-dependence

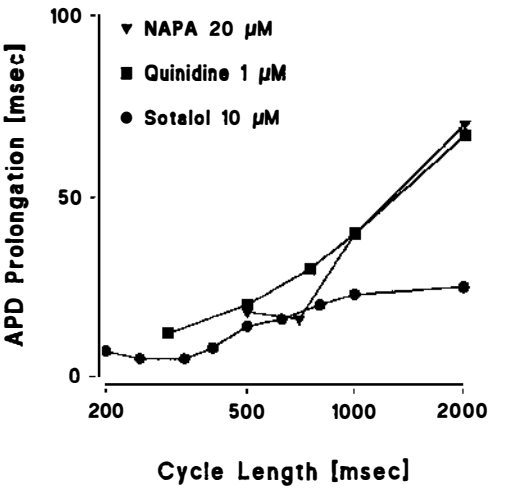

Figure 5 Plot of effects of class III agents on action potential duration at increasing cycle length. (Reprinted with permission from ref 110.).

in human atrial cells for its effects on conduction ($\dot{V}_{max}$) and on action potential duration (57). The authors propose this as an explanation for the efficacy of flecainide in patients with atrial fibrillation.

Another action to activate or open potassium channels has been described for BRL 34915, nicorandil, pinacidil, and several other drugs (58–60). These drugs predominantly relax smooth muscle in vasculature and are used to treat hypertension or angina. However, their effects to open potassium channels can shorten refractoriness of myocardial tissue and lead to an arrhythmogenic state in animal models (61).

Actions on Calcium Currents

Blockade of calcium channels is unlikely to play a role in the prevention or suppression of most clinical ventricular arrhythmias. The exceptions are those arrhythmias involving re-entry within the AV node (9) and the rare forms of monomorphic ventricular tachycardia seen in patients with structurally normal myocardium (62). Although calcium channel blockers appear to be very effective in animal models of reperfusion arrhythmias (63), they have not been found clinically effective for suppression of life-threatening arrhythmias (64). Additionally, most studies have not found them to be effective in reducing mortality or sudden death in patients at increased risk, i.e. populations with recent or acute myocardial infarction (65, 66).

Substantial evidence exists indicating that calcium channel blockers should be effective in blocking arrhythmias caused by early afterdepolarizations (67). The clinical counterpart to these arrhythmias may be torsades de pointes but this has not been reliably determined. Similarities between triggered activity and exercise-induced monomorphic ventricular tachycardia has led to the assumption that delayed afterdepolarizations may play a role in this arrhythmia (68). Some of these patients, particularly those whose arrhythmias cannot be induced by extra stimuli, respond clinically to calcium channel blockers, at least acutely (68). This is confounded by the fact that many calcium channel blockers also have the ability to block sodium channels (69).

Further similarities between the sodium and calcium channel are beginning to emerge. State-dependent blockade of calcium channels has been demonstrated and as a result the principles of the modulated receptor theory have been applied to calcium channels, (40). In this respect, the positively charged analog of the calcium channel blocker D-600, D-890, was active only when placed on the interior of the cell (22), similar to the actions of QX-341 on sodium channels (50). Further similarities between the sodium and calcium channels are likely to become apparent based on the significant degree of sequence homology found between the sodium channels that have been cloned and the dihydropyridine binding site of the calcium channel (70, 71).

Antifibrillatory Actions

Recent studies, both basic and clinical, have supported the thesis that "antifibrillatory" actions of drugs are distinct from "antiarrhythmic actions". This concept was based on the results of experiments by Lucchesi & Hardman (72) and later on the clinical observation that intravenous bolus injections of bretylium could rapidly correct ventricular fibrillation (73). Two quarternary drugs with antifibrillatory actions, clofilium (55) and meobentine (74), have entered clinical testing but were withdrawn because of poor or highly variable oral bioavailability. The mechanism of antifibrillatory actions is poorly understood but is usually seen with drugs that increase refractoriness (Class III action). Cardinal & Sasyniuk (75) proposed that the antifibrillatory action of bretylium was due to its ability to reduce dispersion of repolarization across an ischemic boundary.

Lucchesi and coworkers have developed an animal model for sudden death based on the presence of acute ischemia in a previously scarred ventricle. In this model, acute ischemia in a region remote from the infarct-related artery leads to ventricular fibrillation within one hour in approximately 80% of dogs. Chi et al (76) found that sematilide and CK-3579, drugs with Class III action, reduced the incidence of ventricular fibrillation. Interestingly, flecainide increases susceptibility to ventricular fibrillation in this model and thus provides evidence that this may represent the mechanism of the increased mortality seen with this agent in CAST (77). Likewise, the efficacy of beta blockers in this model may explain their efficacy in reducing mortality in patients with prior myocardial infarction (78).

UNDESIRED ACTIONS OF DRUGS

Proarrhythmia

DEFINITION Although most physicians were aware that antiarrhythmic drugs were capable of causing new or worsened arrhythmias in some patients, in the early eighties reports began to appear in the literature emphasizing the fact that some populations had very high incidences of arrythmia worsening, up to 15–20% with some agents (79). Over the years concern has mounted about the appropriate terminology, the strict definition of these terms, and their applications in research and/or patient care. Many discussions were held about the appropriate use of such terms as "proarrhythmia", "arrhythmogenesis", and "arrhythmia aggravation". The term proarrhythmia is generally accepted as any new abnormal or worsened cardiac rhythm occurring after a drug has been administered. The reader is referred to a recent series of articles for a more thorough consideration of the problem (80). For this review, four forms of proarrhythmia are considered: (*a*) new and/or incessant sustained ventricular tachycardia; (*b*) torsades de pointes; (*c*) new ventricular

fibrillation; and (*d*) the increased incidence of sudden arrhythmic death observed in the CAST study. Other less well-defined occurrences should probably not be included in this definition. A statistically significant increase in the number of asymptomatic PVDs has no clinical significance and may have relevance only when it occurs in a research study. Clinically it should be considered only as evidence of lack of antiarrhythmic drug action. Likewise, the issue of greater ease of induction of arrhythmias during electrophysiologic study is an interesting area of research, but most clinical electrophysiologists admit that they do not know how to interpret or react to such events (81, 82).

TORSADES DE POINTES Historically, one of the first and still most perplexing forms of proarrhythmia is torsades de pointes, originally recognized by Selzer & Wray (83) in 1964 and described by Dessertenne in 1966 (84). This arrhythmia should really be considered a clinical syndrome to distinguish it from polymorphous ventricular tachycardia that is commonly seen in patients with severe ischemic heart disease or cardiomyopathy and lacks the characteristic features seen in torsades de pointes. Torsades de pointes has the characteristic "twisting of the points" that appears as a gradual rotation of the QRS axis around an isoelectric baseline. The syndrome of torsades de pointes has the following features;

1. Gradually changing electrical axis for ventricular depolarization;
2. Preceded by marked prolongation of the QT interval (usually to >500 msec);
3. Occurs in the setting of one or more of the following:
   Drug administration—quinidine or one of many others
   Hypokalemia
   Hypomagnesemia
   Bradycardia
   Congenital long QT syndrome;
4. Is initiated by a long-short sequence of ventricular beats;
5. Is usually nonlethal and self-terminating if accurately diagnosed and appropriately treated;
6. Usually responds to maneuvers to increase heart rate and to normalize serum potassium.

Torsade de pointes has been reported with almost all antiarrhythmic drugs, although predominantly with quinidine. However, since QT prolongation occurs in most patients receiving drugs with subclass IA and Class III actions, it may be difficult to distinguish between torsades de pointes induced by the drug and a spontaneous episode of polymorphous ventricular tachycardia

occurring independently of the drug. A careful search for the other components of the syndrome is helpful in making the distinction.

Although antiarrhythmic drugs are often associated with torsades de pointes, many other drugs including antibiotics (85), psychotropic agents (86), etc, have been reported to induce this syndrome. The common feature of these known agents is that they prolong the QT interval. However, there is no reliable relationship between a drug's potency for prolonging QT and the incidence of torsades de pointes. Most cardiologists would agree that quinidine has the highest incidence but it is also the one most frequently prescribed in the U.S. There are several reports of torsades de pointes occurring during procainamide therapy but most are cases in which plasma concentrations of N-acetylprocainamide (a metabolite with predominantly Class III action) have been documented to be elevated or would be expected to be high, e.g. patients with renal insufficiency given usual dosages. The number of cases reported with disopyramide is much lower than would be expected considering its effects on action potential duration (APD) in vitro. This may be because of the opposing actions of the two isomers on APD and the relatively higher clearance of the isomer that prolongs APD (32, 33).

Much of what has been learned about potential mechanisms of torsades de pointes is derived from studies in animals and isolated tissues. The wealth of evidence indicates that torsades de pointes is the result of EADs (55, 87). Initially EADs appear as small deflections (depolarizing bumps) during the rapidly repolarizing phase 3 of the action potential. A recent clinical report has identified these deflections in the monophasic action potential recordings of a patient with torsades de pointes due to quinidine (Figure 6; 88). They were found to coincide with the prominent U waves and grossly prolonged T waves and were not seen after the drugs were withdrawn and the arrhythmia had dissipated. It is theorized that EADs are caused by intracellular fluxes of calcium because of their in vitro abolition by calcium channel blockers (67). Treatment of torsades de pointes with these drugs has not been tested clinically, probably because of the danger of hypotension or heart block occurring in an already compromised patient. Importantly, most patients respond to less dangerous interventions such as pacing, sodium bicarbonate, isoproterenol, and/or magnesium. In recent years, interest has been renewed in the role of magnesium in treating torsades de pointes (89). After anecdotal case reports described torsades de pointes in the setting of hypomagnesemia (90), several studies found intravenous infusions of magnesium to be effective in suppressing recurrent bouts of torsades de pointes (91, 92). Also, anecdotal reports have found mexiletine (93) or tocainide (94) effective in correcting torsades de pointes. No controlled studies have been performed to prove the efficacy of any intervention or to compare any of those that have been proposed as potentially effective.

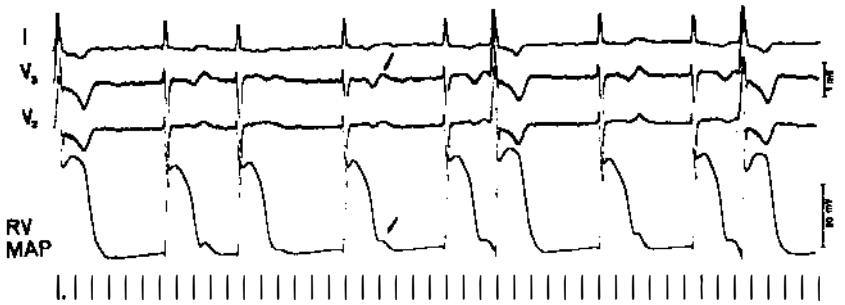

Figure 6 Recording of surface electrocardiographic leads I, V_2, and V_3 and a monophasic action potential from the endocardial surface of the posterior paraseptal region of the right ventricle (RV-MAP). The monophasic action potential shows a distinct hump in phase 3 repolarization (arrow) characteristic of early afterdepolarization. The peak of the early afterdepolarization is synchronous with the peak of the U wave and the amplitude of both waves (arrows) varies significantly with the length of the preceding RR intervals > 1,000 ms and seem to arise close to the peak of the U wave and the early afterdepolarization. Electrocardiographic leads are recorded at twice standard amplitude. (Reprinted with permission from ref. 88.)

The recent information about the possible cellular mechanism for torsades de pointes has several implications. In the future we may be able to treat torsades de pointes with greater effectiveness and safety but perhaps more importantly, we may be able to prevent or at least reduce the incidence of torsades de pointes. A much greater potential benefit would be reaped if, as many suspect, the mechanism of torsades de pointes is similar or related to the events responsible for sudden cardiac death and/or reperfusion arrhythmias.

SUSTAINED VENTRICULAR TACHYCARDIA With the development of new drugs in Subclass IC came the recognition of another form of proarrhythmia, new incessant ventricular tachycardia. Although this condition had been observed with the older agents such as quinidine, procainamide, and disopyramide, it occurred more frequently and was more easily recognized when encainide and flecainide were first being evaluated in patients with severe cardiac disease (95). In an early series, forty percent of patients with a history of life-threatening ventricular arrhythmias developed severe arrhythmia aggravation with encainide. Subsequent recognition of the formation of active and potentially toxic metabolites led to more conservative dosing regimens and the incidence declined to approximately 4–16% (79, 96). Similar experiences have occurred with flecainide (95) and indecainide (97), two other agents with IC characteristics.

The typical form for this type of proarrhythmia is the new onset or more frequent occurrence of sustained monomorphic ventricular tachycardia beginning shortly after initiating therapy or increasing dosage. In patients with a

history of developing sustained monomorphic VT, it may be difficult to discriminate this type of proarrhythmia from spontaneously occurring worsening of the patients' own arrhythmia. It is generally assumed that this form of proarrhythmia is due to the conduction-slowing effects of the drug causing new re-entrant circuits to become enabled.

VENTRICULAR FIBRILLATION Until recently, ventricular fibrillation due to initiation of antiarrhythmic drug therapy has been little appreciated. Minardo et al (98) reported 28 patients with 38 episodes of newly occurring ventricular fibrillation during antiarrhythmic therapy. Although unable to estimate the frequency of this occurrence, they concluded that it is an early event (median duration of therapy = 3 days), that subsequent trials with antiarrhythmic drugs increased the risk of recurrence, and that ventricular dysfunction, diuretics, and digitalis may predispose to this complication. This experience and other proarrhythmic events have led several authors to conclude that initial therapy with antiarrhythmic drugs should be initiated under close electrocardiographic monitoring (99). The mechanism of these events is not understood but is probably unrelated to other forms of proarrhythmia since it was not associated with prolongation of QRS or QT intervals, ischemia, or new congestive heart failure (98).

CAST-LIKE PROARRHYTHMIA A new form of proarrhythmia has been hypothesized as the cause of the increased mortality seen in the CAST trial (1). Unlike new sustained ventricular tachycardia or ventricular fibrillation described above, this increased mortality occurs steadily over time while the patients continue to take the drug (see Figure 1). It occurs in patients who have appeared to "respond" to the drugs, i.e. their ambient ectopy has been suppressed. It is not associated with excessive QRS prolongation, a higher incidence of heart failure, or sustained ventricular tachycardia and, therefore, is not thought to be due to excessive accumulation of drug effect. Because deaths occurred steadily during follow-up of the patients, the presence of some independently occurring associated event, such as new ischemia, has been hypothesized (76, 100). Support for this hypothesis has been found in studies with animal models that found Subclass IC agents to have proarrhythmic potential when combined with acute ischemic events (100).

An additional characteristic of encainide and flecainide that may contribute to increased mortality may be their disparate effects on action potential duration in Purkinje and myocardial tissues (57, 101). These effects would lead to greater dispersion of repolarization at the boundary between these two tissues, a potentially proarrhythmic milieu.

Congestive Heart Failure

Another potential toxicity that has become better recognized in recent years has been the propensity for antiarrhythmic drugs to further depress ventricular function (102). This is probably a reflection of the patient population being treated, i.e. those with severely compromised ventricular function at baseline, and the greater potency of the newer drugs. All drugs that block sodium channels have the capacity to reduce ventricular function in some individuals at some dosage. Blockade of sodium influx by these drugs could lead to reduced Na/Ca exchange and subsequent reduction of intracellular calcium. However, other factors must be considered. Patients with adequate cardiac reserve may not develop congestive heart failure. Likewise, some drugs may have ancillary properties that counteract the negatively inotropic actions of a sodium channel blocker, e.g. the α blockade caused by quinidine (103).

Nevertheless, the incidence of new or worsened congestive heart failure is a significant problem with all available antiarrhythmic agents (102, 104). The incidence for six drugs ranged from 1.6% to 9.3% in a series of 167 patients with coronary artery disease and a history of congestive heat failure in a series reported by Ravid (102). Gottlieb (105) found a very high incidence of worsened heart failure and marked reduction in ventricular function when patients with compensated congestive heart failure were given a 50 mg oral dose of encainide, a relatively large single dose. Few comparative studies have made objective measurements of ventricular function or have been adequately designed to assess relative incidences of new or worsened heart failure. The Cardiac Arrhythmia Pilot Study (CAPS) compared the incidence of heart failure in a randomized placebo-controlled comparison of encainide, flecainide, moricizine, and imipramine in patients treated for one year after myocardial infarction (8). No statistically significant difference in new or worsened heart failure was noted with any of the agents compared to placebo. However, there was a trend toward a higher incidence of heart failure in the patients treated with flecainide (35% vs 25% on placebo).

A comparison of quinidine or sotalol found both drugs to improve ventricular function compared to baseline as assessed by radionuclide ventriculography (103). Most drugs that prolong action potential duration have been found to have a positive effect on inotropy (106), e.g. N-acetylprocainamide (107), sotalol (103) and its non-beta blocking isomer, d-sotalol (L. Soyka, work in preparation). The mechanism of the positive inotropic actions of drugs with Class III action is not understood. It is inversely related to the degree of APD prolongation and is not blocked by reserpine, alpha blockade, or beta blockade (106). As mentioned earlier, the hemodynamic changes seen clinically with a drug are often the summation of multiple and sometimes opposing

actions. Also, the baseline hemodynamic state and/or the presence of other drugs can dramatically influence the hemodynamic response to an antiarrhythmic drug (109).

FUTURE DRUGS

Several new drugs are nearing the final stages of development. Most drugs with Class I activity have been withdrawn from development in the U.S., e.g. diprafenone (Berlex), ACC-9358 (Du Pont), and quinacainol (Rhone-Poullenc). Moricizine was recently approved by the FDA and will be receiving extensive clinical evaluation by US physicians over the next few years. Its overall role in therapy will be greatly influenced by the outcome of CAST-II. If moricizine is found to reduce mortality in CAST-II, it will be given broader use and clinical trials evaluating other agents will surely follow. If it fails to improve mortality, it is unlikely that similar drugs will be tested in the near future. Several mortality trials to evaluate amiodarone are underway around the world and their outcome will also have a significant impact.

Sotalol, a beta receptor antagonist with Class III activity is under review by the FDA and may be available in the future. Several newer agents with predominantly Class III activity are currently being tested in patients with symptomatic arrhythmias such as sustained ventricular tachycardia or supraventricular tachycardia. Figure 7 compares the chemical structures of several drugs with Class III activity. As can be seen, they are chemical analogs of N-acetylprocainamide or d-sotalol and may have similar mechanisms of action. The effects of some of these drugs to reduce ventricular fibrillation in models of sudden death (76) are encouraging and will hopefully lead to development of one or more of these agents for prevention of sudden death.

Hondeghem & Snyders (110) have made suggestions for development of antiarrhythmic drugs with novel electrophysiologic profiles. They suggest that an ideal profile for a drug would consist of use-dependent block of sodium channels with fast diastolic recovery from block (Class IB) and use-dependent prolongation of APD. Of currently available drugs only flecainide has this latter characteristic but lacks the former, i.e. rapid sodium channel recovery. Their model for potassium channels indicates that use-dependent APD prolongation would be seen with a drug that blocks the potassium channel in the open state. This model explains the negative use-dependence (less APD prolongation at faster rates) of N-acetylprocainamide, quinidine, and sotalol as the result of their blockade of potassium channels in the closed state. The approach suggested by Hondeghem & Snyders (110) may lead to the development of new drugs with this exciting profile.

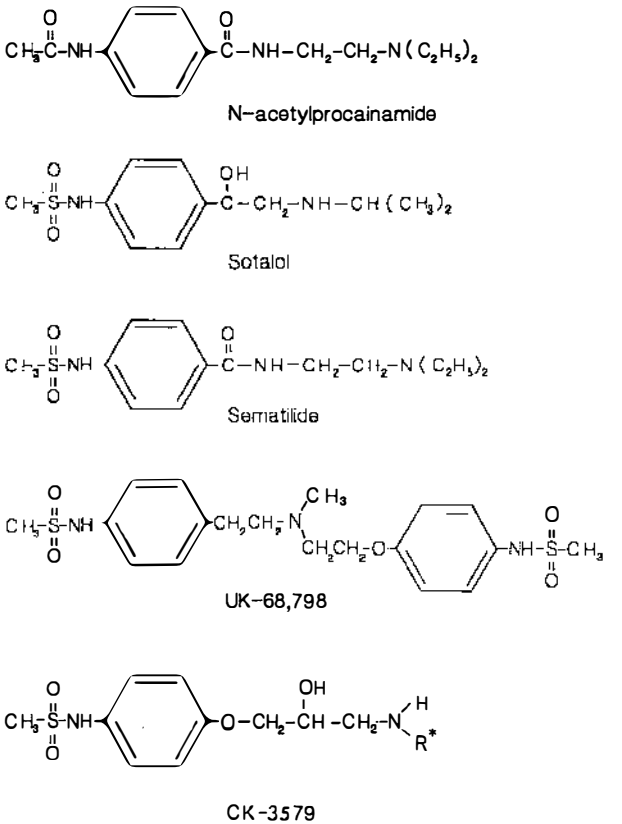

Figure 7 Structures of drugs with predominantly Class III activity:

R = $-CH_2CH_2-O-C_6H_4-C_3N_2H_4$

The majority of arrhythmias are either directly related to myocardial ischemia or occur in patients with damaged myocardium scarred by prior ischemic events. Therefore, the most direct route to prevent arrhythmias will be through efforts to prevent myocardial ischemia. Until coronary artery disease is uniformly prevented, efforts to develop antiarrhythmic drugs should be of clinical value. In the future, understanding the biochemical link between ischemia, membrane currents and arrhythmias should lead to novel approaches.

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