Point of View

Channel Specificity in Antiarrhythmic Drug Action

Mechanism of Potassium Channel Block and Its Role in Suppressing and Aggravating Cardiac Arrhythmias

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The increased mortality associated with the use of the class Ic agents encainide and flecainide in the Cardiac Arrhythmia Suppression Trial (CAST)[1] has led to a critical reexamination of the adequacy of existing therapies for the control of cardiac arrhythmias. Although the reasons for the findings in CAST remain unclear, proarrhythmia due to excessive slowing of conduction has been suggested as a possible contributing cause.[2] Consequently, drugs that act by mechanisms other than sodium channel block, for example, β-blockers and the class III antifibrillatory agents, are currently receiving renewed interest as possible alternative therapies. Although the beneficial effect of β-blockade in postinfarction patients has been clearly established in several randomized trials,[3] much less is known about the efficacy and overall safety of the class III antiarrhythmic agents. Preliminary results, however, suggest that the class III agents generally demonstrate greater efficacy than conventional class I agents in preventing ventricular arrhythmias occurring during acute ischemia or evoked by programmed electrical stimulation, while producing less cardiac depression than other antiarrhythmic drug classes.[4-6]

Available data suggest that most class III agents exert their effects on repolarization by blocking one or more potassium channels.[7] In a recent "Point of View," Hondeghem and Snyders[8] suggest that the therapeutic potential of currently available class III antiarrhythmics is limited by 1) a diminished ability to prolong repolarization at fast heart rates, which would reduce their effectiveness in terminating tachycardias, and 2) a tendency to produce excessive prolongation at slow heart rates, which might lead to proarrhythmia. This pattern of activity, that is, reduced efficacy at fast heart rates and increased efficacy at slow heart rates, is opposite to that typically observed with class I agents,[9] which tend to exhibit greater pharmacological effects (i.e., more conduction slowing) as heart rate is increased. The decline in class III activity at fast heart rates has been attributed to a phenomenon called "reverse" use-dependence,[8] by which potassium channel block is relieved by depolarization and enhanced by hyperpolarization, the reverse of what occurs with the sodium channel blockers. This particular paradigm for potassium channel block is based on an analysis of the effects of the class Ia agent quinidine on delayed rectifier potassium currents in guinea pig ventricular myocytes.[10]

In the present article, we review briefly the role of myocardial potassium channels as targets for class I and class III antiarrhythmic drug action, and suggest a model for the drug-channel interaction that is most consistent with the information currently available on potassium channel block in several different cardiac preparations. Our investigations indicate that potassium channel block by both class I and class III antiarrhythmic agents is enhanced by depolarization and removed by hyperpolarization, and is therefore identical to the type of use-dependence described previously for drug block of sodium channels. This model is supported by direct measurements of delayed rectifier currents in cat ventricular myocytes that are consistent with drug block and unblock of open channels. Finally, we demonstrate that agents that prolong refractoriness by delaying the recovery of sodium channels carry some intrinsic potential for arrhythmia aggravation because they can introduce nonuniformities in otherwise homogeneous tissue by prolonging the diastolic "window" over which slow conduction and unidirectional block can occur. This effect is greatest for kinetically slow drugs like the class Ic agents.

Specificity of K^+ Channel Block

At last count, at least seven different potassium channels have been described in the heart and sug-

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TABLE 1. Specificity of Antiarrhythmic Drugs in Blocking Cardiac Potassium Channels

Class	Agent	I_k	I_{k1}	I_{to}	References
Ia	Quinidine	Yes	Yes	Yes	10, 11, 20, 49, 51
	Disopyramide	Yes	Yes	Yes	12
Ib	Lidocaine	No	No	No	11,12
Ic	Flecainide	Yes	No	No	13
	Encainide	Yes	No	No	Follmer and Colatsky, unpublished
III	Sotalol	Yes	Yes	Yes	52, 53
	Amiodarone	Yes*	Yes†	No	54–56
	Clofilium	Yes*	Yes‡	No	40, 41, 57
	Risotilide	Yes	No	No	58
	E-4031	Yes	No	No	13, 25, 26, 59
	UK-68,798	Yes	No	No	60
	Tedisamil§	Yes	No	Yes	61

Presence of block assessed relative to therapeutically relevant concentrations.

*Appears to block "big" I_k and "little" I_k nonselectively, whereas block by the other class III agents listed appears to be selective for "little" I_k.

†Block of I_{k1} by amiodarone has not been confirmed in cat ventricular myocytes (Follmer and Colatsky, unpublished).

‡The reported absence on an effect of clofilium on I_{k1} may be due to relatively short exposure times (15 minutes) because a tertiary analogue of clofilium is a potent inhibitor of I_{k1}.[41]

§Tedisamil is also reported to block sodium current, especially at higher concentrations.

gested to play a role in normal repolarization. Of these, the delayed rectifier channel (I_k) has been identified as a particularly important target for antiarrhythmic drug action. Most currently available class III agents have been shown to block potassium channels selectively, whereas several class I agents such as quinidine,[11] disopyramide,[12] and flecainide[13] are potent inhibitors of both potassium and excitatory sodium channels. As illustrated in Table 1, some antiarrhythmics tend to be rather nonspecific in their potassium channel blocking effects, whereas others demonstrate reasonably good selectivity for the delayed rectifier current, I_k.

At the present time, it has not been established that selectivity in potassium channel block offers any particular advantage in determining the antiarrhythmic efficacy or proarrhythmic potential of a drug. Indeed, it has been argued that the ionic mechanism by which class III agents prolong repolarization is relatively unimportant, as long as the final result is a net decrease in outward repolarizing current during the plateau.[8] It is reasonable to expect, however, that clinically relevant differences will exist among agents having different ionic mechanisms. For example, drugs that inhibit the inward rectifier current I_{k1} may be more likely to increase diastolic membrane resistance (R_m) and the resting length constant than drugs that lack this activity. The resulting increase in R_m and length constant would increase the extent of electrotonic interactions between cells. This action may be antiarrhythmic, by allowing the action potential upstroke to spread a greater distance and thereby facilitating propagation. Conversely, because a given current can now produce a larger voltage change, cells may also become more susceptible to the depolarizing influence of adjacent tissue, an effect that might favor the appearance of arrhythmias by slowing conduction through inactivation of sodium channels or causing abnormalities in the repolarization time course.[14]

Similarly, drugs that selectively block the transient outward current, I_{to}, may be expected to produce more dramatic increases in action potential duration (APD) at slow heart rates because the slow reactivation kinetics of this current minimize its contribution to the action potential at short cycle lengths.[15] To date, no such agent has been identified (Table 1). Several studies, however, suggest that I_{to} is extremely prominent in atrial myocytes and may be the primary repolarizing current in this region of the heart. Consequently, selective inhibition of I_{to} may, in theory, offer some specificity for the suppression of supraventricular arrhythmias.

Most clinical experience to date has been with class III agents that inhibit the delayed rectifier current. This approach is attractive for several reasons. First, the contribution of I_k to repolarization should be greater at shorter cycle lengths because the slow deactivation of I_k during diastole will result in a progressive accumulation of open (residually activated) channels from one action potential to the next.[16] Second, the effect of agents acting by this mechanism should be amplified in depolarized tissue because the inwardly rectifying properties of the channel will accentuate drug effects at potentials between −60 and −40, at which the fully activated current-voltage relation provides maximal outward current. These considerations support selective block of I_k as a reasonable first approach in the design of new class III antiarrhythmic agents.

Excessive prolongation of repolarization may sometimes be associated with the onset of a polymorphic ventricular tachycardia that can be diagnosed as torsade de pointes.[17] This particular arrhythmia is most commonly induced by the class Ia antiarrhythmics but is relatively rare during therapy with class Ib

and Ic agents. Because experience is more limited, the picture for the class III agents is less clear at this time. Sotalol has been reported to induce torsade de pointes at high concentrations, as well as at lower concentrations, in the presence of hypokalemia or with coadministration of other agents that prolong repolarization.[17] The incidence of torsade de pointes with amiodarone appears to be lower than expected, however, based on its ability to dramatically increase the QT interval.[18]

It is intriguing to speculate that drugs that block multiple channel types exhibit a greater tendency to produce proarrhythmia than drugs that specifically inhibit one channel only. The class Ia agents, which block I_k, I_{k1}, and I_{to} nonselectively, have a high incidence of torsade de pointes. The class Ic agents, encainide and flecainide, inhibit I_k only but produce an incessant polymorphic ventricular tachycardia that is distinct from torsade de pointes in that it is associated with fast heart rates and excessive conduction slowing rather than pauses and QT prolongation. The somewhat greater potassium channel selectivity of amiodarone relative to sotalol may contribute to the apparently lower tendency for amiodarone to produce pause-dependent arrhythmias, although other factors cannot be excluded at this time. Although additional experimental data are needed to evaluate this hypothesis, it is supported by the recent observation that early afterdepolarizations and triggered activity are easier to induce in canine Purkinje fibers studied in vitro by using the nonselective class Ia agents, quinidine and disopyramide, than with risotilide, an investigational class III agent that is a relatively "pure" blocker of I_k.[19] It will be interesting whether clinical studies on the newer, more selective class III agents will ultimately demonstrate an improved safety profile over initial entries in this class.

Quinidine and Other Blockers of I_k Exhibit Conventional Voltage Dependence

Quinidine block of I_k in nodal cells has been shown to exhibit the same type of voltage dependence as found for the sodium channel blockers,[20] that is, 1) block appears to require open channels because voltage clamp depolarizations to membrane potentials below the activation range of I_k produce little or no block, 2) both the level and rate of quinidine block are increased as the membrane potential is made more positive, and 3) repolarization leads to unblocking, as evidenced by a slowing of the decay of I_k tail currents as quinidine dissociates from blocked open channels. Additionally, the I_k activation curve is shifted toward more negative potentials with a steepening in slope, consistent with voltage-dependent drug binding. The actions of quinidine were well fitted by a modulated receptor model with steeply voltage-dependent time constants for block of open channels that decrease from 300 msec at −30 mV to 50 msec at 0 mV.

In our own work, we have found similar effects on I_k tail currents in cat ventricular myocytes with the class Ic agents, encainide and flecainide. This point is illustrated by the tracings shown in Figure 1 (panel A). In the absence of drug, depolarizations to 50 mV completely activate I_k, which then decays on repolarization to −65 mV with a time constant of 208 msec. Encainide reduces the peak amplitude of the I_k tail current to 32% of its control value and slows the deactivation time constant to 322 msec, resulting in a crossover of the control and treatment traces at later times. Additionally, tail currents in the presence of encainide show a distinct rising phase immediately after the repolarization step. Similar behavior has been reported for the quaternary ammonium compounds in nerve,[21,22] and can be explained if the drug prevents channel closure on repolarization and unbinds at negative potentials. The lower panel (Figure 1, panel B) shows the result of a simulation in which this model was tested quantitatively. The predicted current waveform is reasonably close to that obtained experimentally and supports drug interactions with channels in the open state. Additionally, the model predicts that drug unbinding is fast, or at least as fast as the time course of I_k deactivation.

A different picture, however, emerges from studies in guinea pig ventricular cells, in that hyperpolarization appears to increase the level of block, whereas depolarization reduces it.[10] In these experiments, quinidine significantly delayed activation of I_k, as measured by tail current amplitude, without altering the later time course of activation. These results, however, could also be explained if quinidine selectively blocked a small and more rapidly activating component of tail current that is normally buried within the larger I_k.[10,23]

"Big I_k" and "Little I_k"

Recent voltage clamp studies in ventricular myocytes by several investigators have begun to clarify the number and types of delayed rectifier potassium channels present in the myocardial cell membrane. Although some differences exist, the delayed rectifier currents now being described in isolated myocytes are generally similar to those reported by Noble and Tsien[24] in sheep Purkinje fibers, that is, one that activates rapidly and shows marked inward-going rectification, and a second larger component with slow kinetics and a linear fully activated current-voltage relation. Although the characterization of I_{x1} and I_{x2} in sheep Purkinje fibers may have been complicated by problems of external K^+ accumulation and depletion during voltage clamp steps, the presence of two distinct components of I_k with properties similar to I_{x1} and I_{x2} is supported by recent results in chick and guinea pig myocytes. As summarized in Table 2, the two delayed rectifier currents can be further differentiated on the basis of a number of other properties including their sensitivity to isoproterenol,[25] block by specific class III antiarrhythmics like E-4031,[13,25,26] modulation by divalent cations,[27,28] and their tendency to run down during study.[29] The two components have been labeled I_{kr}(for

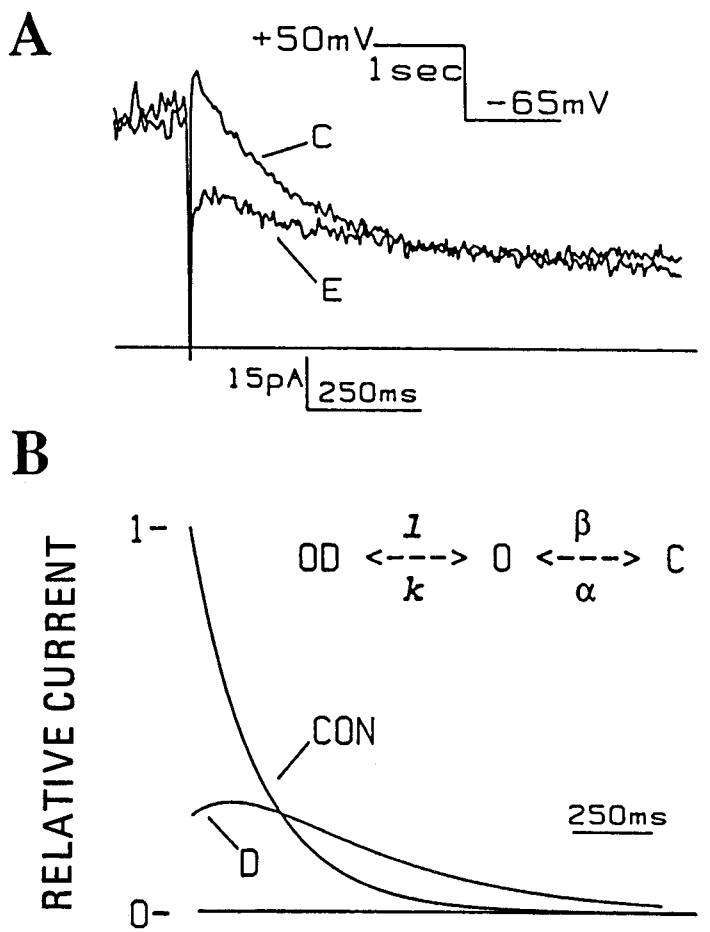

FIGURE 1. *Encainide block of the delayed rectifier I_k in cat ventricular myocytes.* Panel A: *Tracings showing tail currents in response to a 1-second depolarization to + 50 mV before and after exposure to 30 μM encainide. Under control conditions, the tail current reached a peak (50 pA) almost immediately and decayed exponentially (τ = 208 msec) after return to −65 mV. In the presence of 30 μM encainide, the peak tail current was decreased (70%) to 15 pA and the time course of decay slowed (τ = 322 msec). The tail current also showed a distinct rising phase that required 40 msec to reach a peak. These results suggest that block dissipates during the repolarization step, with the rising phase and slowed decay representing unblocking of open channels.* Panel B: *Computer simulation of open channel unblock. This behavior was simulated by using a simple three-state model similar to that proposed by Armstrong,[21] in which OD is the drug-blocked state, O is the drug-free conducting state, and C is the closed nonconducting state of the channel. Transitions from OD to O to C were governed by the rate constants κ, l, α, and β (inset). In the control trace (trace CON), channels were assumed to be fully activated at the end of the depolarizing step (probability of O state occupancy=1), and there were no closed or drug-blocked channels (occupancy for OD and C states=0). The time course of decay was determined by β=0.00486 msec^{-1}, with α, κ, and l set to near 0 or 10^{-6} msec^{-1}. Encainide was assumed to block 75% of the channels, with initial occupancies of OD=0.75, O=0.25, and C=0 (trace D). Rate constants were as follows: κ=0.0002 msec^{-1}, l=0.025 msec^{-1}, β=0.0487 msec^{-1}, and α=10^{-6} msec^{-1}. Although the model assumes open blocked channels must unbind before they can close, drug unbinding without passing through a transient conducting state probably occurs in a fraction of the drug-bound channels. Including a term for this effect would provide a closer fit to the experimental results.*

I_k "rapid") and I_{ks} (for I_k "slow").[26] Both components can be identified in cells from guinea pig,[10,26,30] sheep,[24] and chick,[31] whereas some species appear to exhibit only the fast (cat[32,33] and rabbit[20,34,35]) or slow (frog[36–38]) delayed rectifier subtype.

Most of the newer class III antiarrhythmic agents such as E-4031, UK-68,798, and risotilide appear to block the smaller, inwardly rectifying component of delayed rectifier current preferentially, as do quinidine, flecainide, and sotalol. In guinea pig ventricular cells, which exhibit both types of I_k, E-4031 and sotalol completely inhibit the rapid component without altering the more prominent slow current,[39] whereas the quaternary class III agent clofilium appears to block both.[40,41] In cells with both channel subtypes, drugs selective for the rapidly activating component would suppress tail currents elicited by short depolarizations (which principally activate I_{kr}, not I_{ks}) but not long depolarizations (during which I_{ks} becomes predominant) and introduce an apparent delay in the "activation" of I_k if the global tail currents were being treated as representing a single delayed rectifier current.[10]

Is Class III Activity Relevant at Fast Heart Rates?

The ability of the class III agents to prolong repolarization is diminished at fast heart rates and enhanced by bradycardia.[42] The suggestion has been made recently that these properties seriously compromise the usefulness of the class III agents by reducing their efficacy at the short cycle lengths commonly seen during episodes of substained ventricular tachycardia (400–500 msec), and by promoting proarrhythmia by excessively prolonging the action potential at long cycle lengths.[8] Nevertheless, the weight of available experimental evidence suggests that agents that prolong repolarization without slowing conduction are in fact extremely effective in suppressing tachyarrhythmias evoked by programmed electrical stimulation and episodes of acute myocardial ischemia, whereas class I agents are only moderately effective or even proarrhythmic under

TABLE 2. Differential Characteristerics of the Two Components of Delayed Rectification in the Heart

	"Little I_k"	"Big I_k"
Nomenclature	I_{x1}, I_{kr}, I_{kf}	I_{x2}, I_k, I_{ks}
Species	Guinea pig VM Sheep PF Chick AM Rabbit SA, AV, PF Cat VM ...	Guinea pig VM Sheep PF Chick AM ... ... Frog AM
Rectification	Inward	None (linear)
Isoproterenol	No effect	Increases
Run down	No	Yes
E-4031 block	Yes	No
Divalent cations		
External	Increases	No effect
Internal	?	Decreases

VM, ventricular muscle; PF, Purkinje fibers; AM, atrial muscle; SA, sinoatrial nodal cells; AV, atrioventricular nodal cells.

similar conditions.[4-6] Moreover, there is a growing body of clinical data supporting a greater efficacy of the class III agents against sustained ventricular tachycardia when evaluated in comparator trials against class I agents such as procainamide.[43,44]

These data indicate that the blunted ability of the class III agents to prolong APD at fast heart rates does not greatly diminish their antiarrhythmic efficacy compared with class I agents. One possible explanation is that very rapid heart rates may be less likely to develop when APD is prolonged because the increase in refractoriness will prevent premature beats from triggering reentry, as well as reduce the probability that randomly occurring reentrant circuits will be sustained. It is also possible that decreases in membrane potential will enhance the effects of blockers of I_k on APD because 1) I_k will decay more slowly during diastole in abnormally depolarized cells, allowing it to play a greater role in providing residual outward current for repolarization, and 2) drug will unbind from channels more slowly at less negative potentials because of the intrinsic voltage dependence of the drug-channel interaction.[20] Also, as mentioned previously, depolarization will enhance the contribution of I_k to repolarization because the inwardly rectifying properties of the channel provide maximal outward current over this potential range. Finally, it should be realized that although class III effects are diminished at short cycle lengths, they are nevertheless still present. For example, Steinberg et al[45] report increases in APD of 28% versus 14% for clofilium at cycle lengths of 1,400 and 370 msec, respectively, whereas in other studies, *d*-sotalol increased ventricular effective refractory period in patients by 18% at a cycle length of 500 msec.[46] Similarly, Hayward and Taggart[47] found that the class III effects of sotalol on atrial APD and refractoriness in humans were retained both during overdrive pacing and with premature stimulation. Nevertheless, there is still an apparent paradox in that although frequent depolarizations should enhance class III activity, this is generally not seen in practice. The most likely explanation is that there is not necessarily a direct proportionality between I_k block and action-potential prolongation because the contribution of other channels to repolarization (e.g., calcium channel inactivation) may become increasingly important at short cycle lengths. Further studies using more selective blockers of the different K^+ channels may help to resolve this issue.

Proarrhythmicity Window for Class I Agents

It is well appreciated that the class I agents block the excitatory sodium channel and reduce cardiac excitability and conduction in a time- and voltage-dependent manner, and that changes in refractoriness can be obtained by delaying the recovery of the sodium channel from inactivation.[9] There is necessarily a period of time between full excitability (normal conduction) and full inexcitability (refractoriness), however, during which the cell is only partially excitable and premature stimulation leads to slow conduction and a wide variety of cellular activation patterns.

This situation has recently been simulated (Starmer, Lastra, and Grant, unpublished observations) by using the Beeler-Reuter cardiac action potential model in a long (4 cm) one-dimensional homogeneous cable, and a simple three-state binding scheme for the drug-channel interaction, in which channel block develops progressively as drug binds to a transiently available receptor.[21,48] The cable was stimulated at one end at a cycle length of 1,000 msec, and conduction patterns and refractory periods mapped by probing the diastolic interval with a premature impulse applied to the midpoint of the cable every 10th beat. By using this procedure, an interval of time could be identified during which premature stimulation resulted in nonuniform conduction and unidirectional block (i.e., the vulnerable window). In the absence of a drug, the vulnerable window occurred near the tail of the action potential and was 5 msec in duration. When these calculations were repeated in the presence of a sodium channel blocker with fast recovery kinetics (time constant for drug unbinding, τ_{off}=250 msec), the vulnerable window was shifted to a point 41 msec after repolarization and its duration increased to 8 msec. Simulations of kinetically slower drugs (τ_{off} = 667 msec and 1,250 msec) produced further increases in both refractoriness and vulnerable window that were well correlated with their blocking kinetics (Figure 2, panel A).

These results suggest that sodium channel block can transform a homogeneous substrate into a heterogeneous one, with the attendant potential for the generation of new arrhythmia. Because unidirectional block has been postulated to be a prerequisite for the initiation of reentry, the probability that a randomly timed extrastimulus would produce unidirectional block was used as an index of proarrhythmic potential. This probability was calculated as the ratio

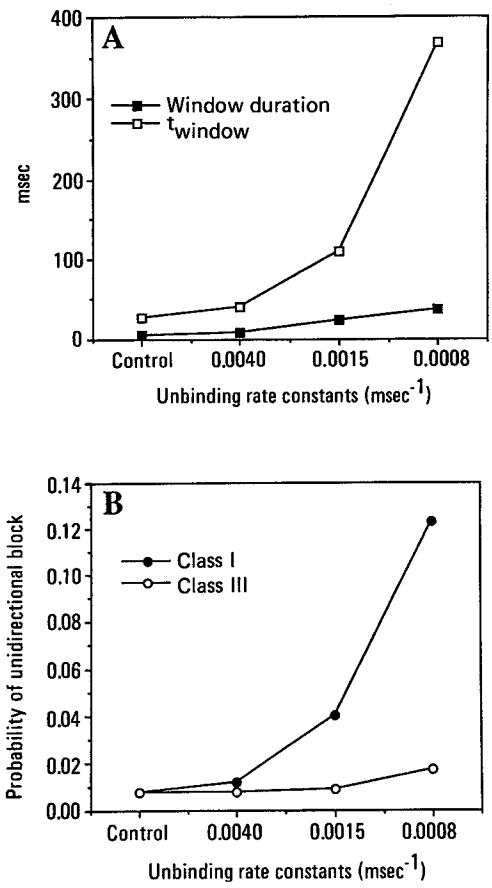

FIGURE 2. *Simulation of the effect of sodium channel blockade on the vulnerable window and the probability of generating unidirectional block.* Panel A: *Change in the duration (closed symbols) and temporal location (open symbols) of the vulnerable window as a function of unblocking rate constants. The time during which unidirectional block could be elicited by extrastimuli in a 4-cm-long cable by using the Beeler-Reuter action-potential model was determined in the presence and absence of sodium channel blockade. Premature stimuli (1 msec, fourfold diastolic threshold) were delivered at the midpoint of the cable after every 10th beat paced at 1 Hz. A simple three-state model was used to describe the drug-channel interaction, with the time course of block defined by the following equation:* $db/dt = \alpha\kappa[D](1-b)/(\alpha+\beta) - lb$, *where b is the fraction of blocked channels,* κ *and l are the rates of binding and unbinding,* α *and* β *are the transition rates between channel conformations with exposed and "guarded" binding sites, and [D] is the drug concentration. Macroscopic sodium conductance is defined by* $gNa \cdot h \cdot (1-b)$, *where gNa is the maximum sodium conductance and h is the Hodgkin-Huxley variable describing channel inactivation. Under the conditions of this simulation, refractory periods were 338 msec (control), 353 msec* ($l=0.004\ msec^{-1}$), *422 msec* ($l=0.0015\ msec^{-1}$), *and 698 msec* ($l=0.0008\ msec^{-1}$). *The binding rate* $\kappa[D]=0.004\ msec^{-1}$ *was the same for each simulation. Temporal location is given relative to the time at which membrane potential crosses −60 mV during repolarization of the preceding action potential.* Panel B: *Probability of eliciting unidirectional block. The probability of eliciting unidirectional block was calculated by dividing the duration of the vulnerable window by the duration of the excitable component of the diastolic interval, as described in the text. The open symbols describe the probabilities obtained by assuming that increases in refractory period occur without changes in window duration.*

of the duration of the vulnerable window to the total diastolic interval available for reexcitation (i.e., the difference between paced cycle length and the refractory period). As shown in Figure 2 (panel B), the likelihood of inducing unidirectional block increases more than 16-fold in the presence of sodium channel blockade, suggesting that the price paid for increasing refractoriness by this mechanism is a greater probability of inducing new arrhythmia, and that this tendency increases directly with the off-kinetics of the drug-channel interaction. The profile for an agent that prolongs refractoriness without slowing conduction is also shown for comparison.

Summary

Although work on class III antiarrhythmics remains at an early stage, these agents still appear to possess greater efficacy and less proarrhythmia than conventional class I agents in those experimental arrhythmia models considered to be most representative of the clinical situation. Although prolongation of repolarization carries with it its own tendency for pause-dependent arrhythmogenesis (i.e., torsade de pointes), available data suggest that this may be a function of nonspecificity in potassium channel block rather than a general characteristic of class III activity. The availability of new and more selective blockers of specific cardiac potassium channels under development as class III agents have already helped to clarify basic questions about the ionic mechanism of repolarization in the heart, and one hopes that a growing clinical data base will eventually determine the relative safety and efficacy of these agents in preventing symptomatic and life-threatening arrhythmias.

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