Class III Antiarrhythmic Agents Have a Lot of Potential but a Long Way to Go
Reduced Effectiveness and Dangers of Reverse Use Dependence

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In a perspective,1 it was pointed out that available class Ic antiarrhythmic agents2 do not discriminate well between normal and depressed tissue and that consequently they are expected to have a lower therapeutic index. The approach to developing more potent antiarrhythmic agents to be tested in patients who do not respond to class IA or IB agents is problematic. Indeed, it is efficacy and safety rather than potency that matters. In fact, simple basic scientific principles suggest that a good sodium channel blocker should interfere markedly with abnormal conduction in tissue responsible for arrhythmias, while leaving the normal conduction intact. Unfortunately, recent data indicate that the concerns for the safety of class Ic agents were justified.3

At present, class III antiarrhythmic agents2 are favored increasingly to treat patients with serious tachycardias. Although these agents could be very powerful antiarrhythmics, our investigation suggests that the currently available drugs have electrophysiologic features that render them relatively less effective than an ideal class III agent could be and may even render them proarrhythmic. We review briefly the kinetic effects on action potential duration of current class III agents. Desirable properties for lengthening of action potential duration are derived, and a simple model illustrating the time- and voltage-dependent actions of a hypothetical compound is developed. Finally, we apply current knowledge of sodium and potassium channel blockade to illustrate how therapy combining class I and class III effects might prove to be especially effective.

Mechanisms Instead of Classification

Class III antiarrhythmic agents are defined as antiarrhythmic drugs that act primarily by prolonging the action potential duration.2 Agents in this category include amiodarone,4 sotalol,5 N-acetylpromacamide (NAPA),6 melperone,7 and several other experimental agents. It is believed that these agents act primarily by blocking cardiac potassium channels, thereby reducing repolarizing currents and prolonging action potential duration.8

Amiodarone is usually classified as a class III antiarrhythmic agent, but it also has class I (blocks sodium channels9,10) class II (antiadrenergic actions),11 and class IV effects (blocks calcium channels).12 Similarly, many of the class I agents, noticeably the class Ic agents, not only block sodium channels but also lengthen action potential duration (e.g., quinidine, procainamide, and disopyramide). Moreover, for drugs with multiple mechanisms of action, it is difficult if not impossible to indicate the primary classification unequivocally. Quinidine, for example, causes both cycle length–dependent widening of the QRS-complex and lengthening of action potential duration. However, whereas the sodium channel block is most marked at fast heart rates and nearly nonexistent at slow heart rates,13 the prolongation of the action potential duration is most marked at slow heart rates.14,15 As a result, quinidine could be labeled primarily as a class III agent at slow heart rates or as a class I agent at fast heart rates. For this reason, it is preferable to discuss mechanisms of drug action, rather than drug classification. Thus, we concentrate on drugs that lengthen action potential duration (class III effects) rather than on class III agents.

Although lengthening of action potential duration can also be achieved by increasing inward currents, we limit our considerations to block of outward currents. Furthermore, although the heart has numerous potassium channels, we concentrate our discussion on the delayed outward rectifier current and use it as an example of an important determinant of action potential duration. However, the principles presented could be applied equally well to the other potassium or outward currents and inward currents as well. Indeed, class III effects merely require a relative reduction in outward currents or increase in

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inward currents. Furthermore, the latter do not necessarily require an increase of peak inward current. For example, slowing of inactivation of the sodium or the calcium current resulting in more inward current toward the end of the action potential could also lengthen the action potential duration.\textsuperscript{16,17} Thus, clearly class III effects must not be equated with potassium channel block.

**Time- and Voltage-Dependence of Drug Effects**

It is now well established that the interaction of sodium and calcium channel blockers with their receptor is time- and voltage-dependent and can be accounted for in terms of the modulated receptor hypothesis.\textsuperscript{18} More recently, our laboratory demonstrated that the interaction of quinidine with the time-dependent outward current also is modulated by time and voltage; quinidine primarily reduces the outward current at negative membrane potentials, and block becomes less pronounced during depolarization.\textsuperscript{8} Thus, this use-dependent block of potassium channels exhibits reverse use dependence; block increases during diastole (phase 4) and declines during the plateau, resulting in less block with increasing use. This contrasts with its use-dependent block of sodium channels that primarily develops during depolarization (upstroke of the action potential) and declines during diastole.

Reverse use dependence accounts nicely for the observation that the prolongation of action potential duration by quinidine is most marked at slow heart rates\textsuperscript{14,15} (Figure 1). Most antiarrhythmic agents that lengthen action potential duration (e.g., sotalol,\textsuperscript{5} NAPA,\textsuperscript{6} and melperone\textsuperscript{7}) exhibit reverse use dependence similar to that of quinidine. Thus, they prolong action potential duration at normal heart rates, but the magnitude of the prolongation declines as heart rate is increased (Figure 1).

Amiodarone\textsuperscript{19} when administered chronically forms an exception: It lengthens action potential duration at normal and at fast heart rates to a similar extent (Figure 2) (i.e., its action appears to be less time and voltage dependent). Under voltage-clamp conditions, amiodarone, contrary to quinidine, does not preferentially bind at negative membrane potentials. If anything, block increases during depolarization instead.\textsuperscript{20}

**Optimal Electrophysiologic Characteristics for Class III Effects**

As a result of reverse use dependence, many drugs with class III properties experimentally have the least effect during tachycardias. Conversely, during bradycardia or after a long diastolic interval (e.g., compensatory pause after an ectopic), these drugs induce maximum prolongation of action potential duration. Excessive lengthening of the QT interval with these agents has been associated with the development of torsade de pointes.\textsuperscript{13} Thus, drugs exhibiting reverse use dependence may become proarrhythmic after long diastolic intervals and become less effective in lengthening action potential duration at short cycle lengths. Despite these shortcomings, agents with predominantly class III properties appear to be moderately clinically effective, perhaps by reducing the diastolic window during which a tachycardia can be initiated.

Theoretically, the efficacy of agents with class III properties could be increased. Indeed, common sense dictates that agents that lengthen action potential duration optimally should elicit relatively little action potential prolongation of the normal heart beat, but maximally prolong action potential duration of ectopics and tachycardias. Thus, as diagrammatically illustrated in Figure 2 (dashed line), the normal cycle-length dependence of action potential duration could remain intact for physiologic heart rates. However, when heart rates exceed a threshold (arrow in Figure 2), the action potential would become increasingly longer causing the termination of the tachycar-
dia. Equally important, an agent with such an electrophysiologic profile would not lengthen excessively the action potential duration after long diastolic intervals and, hence, would be less prone to precipitate torsade de pointes. As for sodium channel blockers, this action potential prolongation could be use dependent; little or no lengthening would occur at normal heart rates, but during a tachycardia a beat-by-beat prolongation would develop until the tachycardia was terminated.

Model

Use-dependent block of open and closed states has been modeled for sodium and calcium channels. To test whether it also can occur for potassium channels such as the delayed outward rectifier and to illustrate the kinetic differences between blockers of rested and open channels, we implemented a modulated receptor\textsuperscript{18} model for potassium channel block. This model allows us to test whether it is at least theoretically possible to have an open channel blocker with an electrophysiologic profile that would approach the optimal drug effect presented above.

Briefly, potassium channels were modeled to exist in two primary states: closed (C) at negative potentials and open (O) at plateau potentials as described in the Beeler and Reuter model.\textsuperscript{16} In reality, there may be multiple closed or open states,\textsuperscript{21} but for the purpose of the present computations these two primary states should be adequate. Transition between the two states was governed by voltage-dependent rate constants. Both states may interact with drug to form RD and OD states (see "Appendix") using characteristic (k\textsubscript{R}, l\textsubscript{R}, k\textsubscript{O}, and l\textsubscript{O}) rate constants. Drug-associated channels do not conduct potassium. We incorporated these equations into the Beeler and Reuter action potential model\textsuperscript{16} (although the results would be qualitatively similar if another model were used) of the cardiac action potential and computed drug effects on action potential duration.

Under drug-free conditions, the action potential duration shortened as heart rate was increased. On addition of an agent that binds primarily to the rested state, action potential duration was increased over the range of normal cycle lengths (600–1,000 msec). Moreover, with increasing heart rate, the prolongation of action potential duration declined, whereas the prolongation increased for longer cycle lengths (see Figure 3). This behavior is very similar to that of quinidine, sotalol, and NAPA (Figure 1).

When computing the effects on action potential duration for an open channel blocker, drug concentrations that gave relatively little lengthening of action potential duration at normal heart rates gave even less prolongation at slow heart rates. However, as a tachycardia developed, action potential duration prolonged markedly, and it was no longer possible to sustain a tachycardia of cycle lengths less than 400 msec (Figure 3). In other words, such tachycardia would become self-terminating.

Combination of Potassium and Sodium Channel Block

In the above descriptions, we have concentrated on drug effects on action potential duration. In reality, maximal tachycardia rate of reentry arrhythmias is determined by conduction velocity and effective refractory period. Although action potential duration is an important determinant of the effective refractory period, availability of sodium current is an additional important parameter. Because recovery from block for sodium channels occurs primarily at negative potentials,\textsuperscript{18} recovery mainly starts after repolarization. Hence, its contribution to lengthening of refractoriness is added to that resulting from prolongation of action potential duration. Thus, prolongation of action potential duration and sodium channel block that by themselves could not adequately prolong refractoriness to prevent or terminate a tachycardia (e.g., because of side effects) might in combination succeed to accomplish this therapeutic goal.

The combination of a drug that exhibits use-dependent block of sodium channels with fast diastolic recovery from block (class I\textsubscript{B}) and one that exhibits normal use-dependent (not reversed) prolongation of action potential duration (not yet available) may markedly extend refractoriness in a use-dependent fashion. However, conduction of the normal heart beat and its duration would be left relatively undisturbed. This condition is somewhat approximated by amiodarone: It has class I\textsubscript{B} (fast recovery from block during diastole) sodium channel–blocking properties\textsuperscript{10} and can sustain its action potential prolongation effects at fast heart rates.\textsuperscript{19} Moreover, the fact that prolongation of the action potential duration is not increased much by bradycardia probably accounts for the fact that torsade de pointes occurs relatively rarely with this agent.\textsuperscript{22} We anticipate that should its class III effects be aug-
mented by fast heart rates, it would be even more effective against tachycardias.

**Summary**

With regard to currently available class III agents, although their class III effect may reduce the likelihood of tachycardia initiation, their reverse use-dependent prolongation of action potential duration reduces their effectiveness during tachycardias and may even render them proarrhythmic, especially after long diastolic intervals. In contrast, agents that exhibit normal use-dependent prolongation of refractoriness hold great promise: While having relatively less effects on the normal heart, they could induce self-termination of a tachycardia. Prolongation of refractoriness can be achieved by lengthening of action potential duration and delaying recovery of excitability. Combination of these drug actions may yield important clinical applications.

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**Appendix**

The Beeler-Reuter model was used to calculate cardiac ventricular action potentials, which were integrated using an improved Euler scheme. The action potentials were initiated by a 2-msec “stimulation” pulse of 20 µA/cm² at the frequency of the various trains. For all trains, the initial priming values for membrane potential, kinetic parameters, and [Ca²⁺], were set to their end-diastolic values for a steady-state 1-Hz train of action potentials, either in control or for the various drug modeling runs. Therefore, the calculations simulate the effect of an abrupt change in cardiac rate from the 1-Hz steady state in control or drug. Drug effects were modeled on the delayed rectifier (called I₅ in the Beeler-Reuter model). Rested state block was modeled as occurring through a lipophilic pathway:

\[
\begin{align*}
R & \xrightarrow{\alpha_{nl}} O \\
\beta_{nl} & \nonumber \\
k_{R}[D] & \xrightarrow{l_{R}} OD \\
\end{align*}
\]

with the following voltage-dependent rate constants:

\[
\begin{align*}
k_o[D] & = k_o(0) \exp (\delta zFE/2RT) \\
l_o & = l_o(0) \exp (\delta zFE/2RT) \\
k_0(0) & = 50/M/msec \\
l_0(0) & = 0.0001/msec \\
\delta & = 0.5 \\
\end{align*}
\]

\[D] = 2 \mu M\]

R, T, F, and z have their usual meaning, and δ represents the fractional electrical distance (the fraction of the membrane field seen by the charged drug at the receptor site on the open channel; the arbitrary value δ = 0.5 assumes that the binding site is halfway into the electrical field). Action potential duration was determined as the time interval between upstroke and repolarization to −75 mV, which for this model approximates 90% repolarization.

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