Frequency-dependent effects of amiodarone on atrioventricular nodal function and slow-channel action potentials: evidence for calcium channel-blocking activity

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ABSTRACT The purpose of these experiments was to determine the frequency dependence of the effects of amiodarone and its active desethyl metabolite on slow-channel tissues. Intravenous amiodarone and desethylamiodarone (10 or 25 mg/kg) increased atrioventricular conduction time (AVCT) and refractory period (AVERP) in open-chest, chloralose-anesthetized dogs. Drug effects on AVCT and AVERP were greatly augmented by increasing atrial stimulation frequency. The frequency dependence of drug effects was quantified by studying the response of atrioventricular (AV) conduction to changes in coupling interval. Under control conditions, premature atrial stimulation increased AVCT with a time constant of 70 msec. In the presence of amiodarone and desethylamiodarone, a biexponential relationship between AVCT and coupling interval was observed. One component had a time constant similar to control, and a slower component with a time constant of about 1 sec appeared. Slow-channel action potentials produced in canine cardiac false tendons by elevated potassium (25 mM) and isoproterenol in vitro showed interval-dependent changes in \( V_{\text{max}} \) with a time constant averaging 74 msec in the absence of amiodarone. In the presence of amiodarone, a slower recovery phase of \( V_{\text{max}} \) with a time constant averaging 0.94 sec was observed. These results indicate that amiodarone and its metabolite produce heart rate-dependent changes in AV nodal function in vivo and suggest use-dependent calcium-channel blockade as a mechanism of this action. Amiodarone’s rate-related effects on slow-channel properties should produce selective depression of supraventricular tachyarrhythmias involving rapid activation of the AV node.


AMIODARONE has recently been approved for the treatment of resistant ventricular tachyarrhythmias in the United States and Canada. This agent is recognized as having great efficacy in the treatment of a wide variety of tachyarrhythmias, both ventricular and supraventricular. The first described clinical use of amiodarone was as an antianginal agent. Subsequently, the classical identification of the class III action of amiodarone by Singh and Vaughan Williams led to the use of amiodarone in treating cardiac arrhythmias. The complexity of understanding amiodarone’s electrophysiologic actions was increased by studies showing it to be a sodium-channel blocker.

Amiodarone’s beneficial effects against supraventricular arrhythmias are predominantly due to a depressant effect on the atrioventricular (AV) node. This action, along with the antihypertensive, antianginal, sinus node-slowing, and occasional negative inotropic effects of amiodarone have been attributed to a non-competitive adrenergic blocking action of the drug. The electrophysiologic effects of intravenous amiodarone are known to differ from the effects of long-term oral amiodarone therapy. Short-term intravenous amiodarone administration alters sinus and AV node properties with little, if any, effect on fast-channel tissues, whereas long-term oral amiodarone importantly increases refractory period and slows conduction in fast-channel tissues. We have shown that accumulation of amiodarone’s desethyl metabolite is responsible for much of this long-term effect on fast-
channel tissues. In the course of the latter experiments, we found that both desethylamiodarone and amiodarone produced frequency-dependent slowing of AV node conduction. These use-dependent effects on AV conduction were similar to changes we had previously observed using a similar experimental preparation to study the actions of calcium-channel blockers. This led us to hypothesize that amiodarone and its metabolite produce interval-related depression of calcium channel-dependent tissues. The present experiments were designed to characterize the time dependence of the depressant effects of amiodarone and desethylamiodarone on AV conduction in vivo and on slow-channel action potentials in vitro. Preliminary results of this work have been presented in abstract form.

Methods

General methods

Experiments in vivo. Mongrel dogs of either sex were anesthetized with morphine (2 mg/kg im) and α-chloralose (100 mg/kg iv). Catheters were inserted into both femoral arteries, and both femoral veins were kept patent with heparinized saline (0.9%). Dogs were ventilated via an endotracheal tube at a rate of 10/min with a tidal volume obtained from a nomogram relating body weight to minute ventilation. Arterial blood gases were measured to ensure adequate oxygenation (SaO2 > 90%) and physiologic pH (7.38 to 7.45). A right thoracotomy was performed and two bipolar Teflon-coated stainless-steel electrodes were inserted into the right atrial appendage for recording and stimulation. A Statham P23 1D transducer (Statham Medical Instruments, Los Angeles), electrophysiologic amplifiers, and a paper recorder (Siemens Mingograf 80 recorder) were used to record blood pressure, electrocardiographic leads and aVR, a right atrial electrogram, and stimuli artifacts. Stimulation was applied with 4 msec square-wave pulses at twice diastolic threshold current. The pulses were delivered through an intramuscular (right atrial) bipolar stainless steel electrode insulated with Teflon except at the tips. Stimuli were controlled by a programmable stimulator connected to a stimulus isolator (Caltronics, Inc.).

Autonomic blockade was achieved by a previously developed regimen. This consisted of a single 1 mg iv dose of atropine and an initial dose of 0.3 mg/kg iv propranolol followed by 0.45 mg/kg/hr propranolol as a continuous intravenous infusion.

Experiments in vitro. Mongrel dogs were anesthetized with pentobarbital (30 mg/kg iv) and their hearts were removed via a right thoracotomy. Ventricular fibrillation was induced electrically to facilitate tissue dissection, and free-running false tendons were removed along with subjacent ventricular muscle and pinned to the Sylgard-covered bottom of a Lucite tissue bath. The false tendons were initially superfused with Tyrode’s solution containing (in mM): Na+, 141; HCO3-, 22; dextrose, 10; K+, 4; Mg2+, 0.5; H2PO4-, 0.9; Ca2+, 2.7; and Cl-, 128. The solution was aerated with 95% O2/5% CO2, resulting in a mean pH of 7.3 in the tissue bath, and the temperature in the bath was maintained at 36°C ± 0.2°C by a feedback-controlled proportional power supply. The preparation was stimulated at a selected frequency by 2 msec twice diastolic threshold, square wave pulses delivered through bipolar platinum electrodes. A stimulus isolator controlled by a programmable stimulator (Bloom Associates, Flying Hills, PA) was used as a current source. Transmembrane action potentials from Purkinje fibers in the false tendon were monitored by standard microelectrode techniques with signals displayed on a Tektronix 5115 storage oscilloscope.

After a 1 hr equilibration period, slow-channel action potentials were produced by a modification of a previously described technique. Superfusate potassium concentration was increased to 25 mM by equimolar substitution of KCl for NaCl in the superfuse. Isoproterenol was administered in 0.1% ascorbic acid by an infusion pump into a mixing chamber in the inflow to the tissue bath to produce a final isoproterenol concentration of 0.125 μM in the bath. The resulting slow-channel action potentials had a mean resting potential of -41 ± 2 mV, action potential amplitude of 62 ± 9 mV, action potential duration to 95% repolarization (APD95) of 152 ± 35 msec, and maximum upstroke velocity of 6.4 ± 1.3 V/sec (all measured at a frequency of 1 Hz). An electronic differentiating circuit with a linear output over the input range of 1 to 20 V/sec was used to measure Vmax of slow-response action potentials. Protocol

Experiments in vivo. The region of the sinus node was crushed to allow for control over atrial response over a wide range of atrial stimulation rates. The atria were paced with square wave pulses of 4 msec duration and twice diastolic threshold current. The pulses were delivered through an intramural (right atrial) bipolar stainless steel electrode insulated with Teflon except at the tips. Stimuli were controlled by a programmable stimulator connected to a stimulus isolator (Caltronics, Inc., Indianapolis). A paper recorder (Siemens Mingograf 80) was used to record blood pressure, stimuli artifacts, and several electrocardiographic leads simultaneously. In seven dogs (three high-dose desethylamiodarone, two high-dose amiodarone, one with low doses of either agent), a His bundle electrogram was monitored from an epicardial approach. AV conduction time (AVCT) was measured from the stimulus artifact to the onset of ventricular activation on the surface ECG. The latency to atrial activation was measured from the stimulus artifact to the onset of the atrial electrogram. The AH and HV intervals were measured from the onset of the atrial electrogram in the His recording to the first rapid deflection in the His bundle electrogram and from the His electrogram to the first recorded ventricular activity, respectively. All recordings were obtained at 250 mm/sec paper speed and were accurate to ± 2 msec. The frequency dependence of AV conduction and refractoriness were determined by pacing the atrium at a variety of basic cycle lengths between 300 and 1000 msec. After at least 2 min of continuous stimulation at each cycle length, AVCT was measured and the effective refractory period of the AV conducting system (AVERP) was determined by the extrastimulus technique. The AVERP was defined as the longest S1S2 interval failing to produce a ventricular response during atrial pacing. When atrial refractoriness was limiting, the atrial ERP was taken as an upper estimate of the AV nodal ERP value. The interval dependence of AV conduction was determined by pacing the atrium at a rate just below the Wenckebach frequency and introducing a pause of varying duration after every 20 basic stimuli.

The above measurements were obtained under control conditions and repeated 60 min after the administration of amiodarone or desethylamiodarone. Doses of 10 or 25 mg/kg of either agent were administered over 20 min, dissolved in 2 ml of 50% ethanol. Only one dose of one agent was studied in each dog. This vehicle for amiodarone administration has previously been shown to have no effect on the variables measured in these experiments. Amiodarone and desethylamiodarone were obtained as the purified hydrochloride salts from Sanofi Research, Inc., and kindly supplied by Ayerst Laboratories, Montreal, Canada.

Experiments in vitro. After slow-channel action potentials

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had been produced as described above, action potential characteristics were followed for at least 30 min to ensure their stability. Amiodarone was then added to the superfusate at a concentration of 5 µM. The amiodarone was constituted as previously described by Ikeda et al., with 6.8 mg of amiodarone dissolved in 1 ml of ethanol, and added to 9 ml of fresh-frozen sheep plasma. Five milliliters of the resulting solution were added to each liter of superfusate to produce the desired amiodarone concentration. The onset of electrophysiologic changes was delayed and variable upon superfusion with amiodarone, and measurements were made at 30 min intervals until clear changes were observed. This occurred an average of 2.5 hr after the onset of amiodarone superfusion. Because of the possibility of time-related changes in the preparation, parallel control experiments were performed in an identical fashion but with only the diluent for amiodarone administration being added to each liter of superfusate to produce the desired concentration. Continuous impalement of a single cell was maintained throughout the observation period.

Action potential characteristics were measured before and after superfusion of amiodarone or its vehicle. In addition, the kinetics of changes in \( V_{\text{max}} \) were determined by observing the response to premature stimuli. The preparation was paced at a basic cycle length of 5 sec, and premature stimuli were introduced after every six basic activations. The \( V_{\text{max}} \) of premature responses were related to their coupling interval, and the time constants characterizing the observed interval dependence were characterized as described below. Only activations arising from full repolarization were analyzed to avoid possible contamination by voltage-dependent effects.

**Analysis of data.** The time constant of interval-dependent changes in AV nodal conduction time and \( V_{\text{max}} \) of slow-channel action potentials were determined by nonlinear least-squares regression to a monoequponential model. Biexponential curve fitting was performed to analyze the dependence of AV conduction time on coupling interval after the administration of amiodarone or desethylamiodarone. Changes in \( V_{\text{max}} \) of slow-channel action potentials after the administration of amiodarone were usually a monoequponential function of coupling interval and were so analyzed. In two experiments, a biexponential analysis was required to fit the data (see Results).

Comparisons between groups of data were performed by analysis of variance with a Scheffé test for multiple comparisons. Unpaired t tests were used for single comparisons between two groups of unpaired data. Group data are represented in this manuscript as mean ± SD unless otherwise indicated. A probability of less than 5% was taken to indicate statistical significance.

**Results**

**Changes in AV conduction and refractoriness.** Both amiodarone and desethylamiodarone slowed AV conduction and increased the refractory period of the AV conducting system (table 1). Drug-induced changes in these variables were frequency dependent, with substantially larger changes occurring at greater activation frequencies. Experiments in which His bundle recordings were available showed that use-dependent changes in AV conduction time were caused by alterations in AH interval (figure 1). Drug-induced changes in AV refractoriness resulted from changes in refractory period of the AV node in experiments with His bundle recordings.

**Use-dependence of changes in AV conduction time.** Under control conditions, AH interval and AV conduction time were a monoequponential function of coupling interval with a time constant in the range of 70 msec (figure 2). In the presence of amiodarone and its metabolite, the relationship between AVCT and coupling

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**TABLE 1**

Effects of amiodarone and desethylamiodarone on AV conduction and refractoriness.

<table>
<thead>
<tr>
<th>Basic cycle length (msec)</th>
<th>400</th>
<th>500</th>
<th>700</th>
<th>1000</th>
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<tr>
<td><strong>AVCT</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>A10 Control</td>
<td>125 ± 17</td>
<td>124 ± 14</td>
<td>120 ± 20</td>
<td>117 ± 22</td>
</tr>
<tr>
<td>A10 Drug</td>
<td>124 ± 14</td>
<td>120 ± 12</td>
<td>151 ± 19</td>
<td></td>
</tr>
<tr>
<td>A25 Control</td>
<td>134 ± 7</td>
<td>130 ± 5</td>
<td>128 ± 4</td>
<td></td>
</tr>
<tr>
<td>A25 Drug</td>
<td>130 ± 5</td>
<td>158 ± 15</td>
<td></td>
<td></td>
</tr>
<tr>
<td>D10 Control</td>
<td>139 ± 11</td>
<td>132 ± 11</td>
<td>131 ± 13</td>
<td></td>
</tr>
<tr>
<td>D10 Drug</td>
<td>128 ± 13</td>
<td>168 ± 20</td>
<td></td>
<td></td>
</tr>
<tr>
<td>D25 Control</td>
<td>147 ± 12</td>
<td>128 ± 13</td>
<td>170 ± 22</td>
<td>228 ± 35</td>
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<tr>
<td>D25 Drug</td>
<td>147 ± 12</td>
<td>151 ± 19</td>
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<td></td>
</tr>
<tr>
<td><strong>AV refractory period</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>A10 Control</td>
<td>153 ± 21</td>
<td>168 ± 22</td>
<td>170 ± 22</td>
<td>228 ± 35</td>
</tr>
<tr>
<td>A10 Drug</td>
<td>152 ± 21</td>
<td>245 ± 49</td>
<td></td>
<td></td>
</tr>
<tr>
<td>A25 Control</td>
<td>160 ± 14</td>
<td>168 ± 13</td>
<td>180 ± 14</td>
<td>255 ± 45</td>
</tr>
<tr>
<td>A25 Drug</td>
<td>160 ± 14</td>
<td>273 ± 61</td>
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<tr>
<td>D10 Control</td>
<td>173 ± 34</td>
<td>190 ± 38</td>
<td>195 ± 35</td>
<td>205 ± 62</td>
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<tr>
<td>D10 Drug</td>
<td>173 ± 34</td>
<td>197 ± 54</td>
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<td></td>
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<tr>
<td>D25 Control</td>
<td>150 ± 22</td>
<td>158 ± 26</td>
<td>160 ± 24</td>
<td>238 ± 13</td>
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<tr>
<td>D25 Drug</td>
<td>150 ± 22</td>
<td>235 ± 37</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

A10 = effect of 10 mg/kg amiodarone (n = 8 dogs); A25 = 25 mg/kg amiodarone (n = 5 dogs); D10 = 10 mg/kg desethylamiodarone (n = 6 dogs); D25 = 25 mg/kg desethylamiodarone (n = 5 dogs).

*Values shown are AVCT or refractory periods (msec) before and after drug administration.

*Insufficient data for presentation.

*p < .05; †p < .01; ‡p < .001, compared with corresponding control by analysis of variance with Scheffé contrasts.

*Values in parentheses are not significantly different from control.
interval became clearly biexponential (figure 2). The terminal phase of conduction slowing had a time constant ($t_{\text{slow}}$) in the range of 1 sec in the presence of both amiodarone and its metabolite (table 2). In contrast, the more rapid phase of conduction slowing in the presence of these agents had a time constant ($t_{\text{fast}}$) in the range of 90 msec, which was similar to the time constant of conduction slowing before drug administration. With long pauses (> 5 sec) there was full recovery from amiodarone-induced conduction slowing and AVCT reached control values.

**Changes in action potential characteristics of slow-channel action potentials.** Figure 3 shows typical slow response action potentials before and after superfusion with amiodarone. The only variable that changed significantly upon amiodarone superfusion was $V_{\text{max}}$, which amiodarone reduced in a frequency-dependent fashion. Superfusion with the vehicle for amiodarone was also associated with a decrease in $V_{\text{max}}$ over a comparable observation period but without any frequency-dependent component. When changes in $V_{\text{max}}$ produced by amiodarone were compared with the results of vehicle superfusion (figure 4), amiodarone produced significantly greater depression at activation frequencies of 86 and 120/min.

Before amiodarone superfusion, changes in $V_{\text{max}}$ of slow-channel action potentials were an exponential function of coupling interval (figure 5). The time constant of this process averaged 74 msec (table 2). After amiodarone, the rate of change in $V_{\text{max}}$ became much slower. In two experiments, a biexponential relationship was observed in the presence of amiodarone, as shown in figure 5. For both of these experiments, the rapid phase of $V_{\text{max}}$ slowing in the presence of the drug had the same time constant as changes in $V_{\text{max}}$ before drug superfusion, whereas the slower phase of $V_{\text{max}}$
change had a time constant in the range of 1 sec. In five other experiments, only a slow phase of $V_{\text{max}}$ change was observed in the presence of amiodarone, with refractoriness occurring before the onset of any rapid alterations in $V_{\text{max}}$. The mean slow phase time constant for changes in $V_{\text{max}}$ in the presence of amiodarone (for all seven experiments, 940 msec) was in the same range as the slow phase of recovery of AV conduction time in the presence of amiodarone in vivo (table 2). Superfusion with the vehicle for administration of

### TABLE 2

<table>
<thead>
<tr>
<th>Interval dependence of changes in AVCT before and after administration of amiodarone and desethylamiodarone*</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\tau_1$</td>
</tr>
<tr>
<td>Control</td>
</tr>
<tr>
<td>A10</td>
</tr>
<tr>
<td>Control</td>
</tr>
<tr>
<td>A25</td>
</tr>
</tbody>
</table>

*Changes in AVCT were fitted to a relationship of the form $\Delta V_{\text{CT}} = Ae^{-C t} + Be^{-C t}$, where $\Delta V_{\text{CT}}$ = difference between AVCT at coupling interval (CI) and AVCT at the longest pause obtainable. For control conditions, a monoexponential relationship was observed and $B$ was set to zero.

Interval dependence of changes in $V_{\text{max}}$ of slow-channel action potentials before and after amiodarone superfusion in vitro: $\tau_1$ (control), 74 ± 36 msec; $\tau_2$ (Amio), 940 ± 421 msec. Changes in $V_{\text{max}}$ were similarly fitted to an equation of the form $\Delta V_{\text{max}} = Ae^{-C t} + Be^{-C t}$, $B = 0$ for control conditions and $A = 0$ in the presence of amiodarone for all but two experiments.

![Figure 2](http://circ.ahajournals.org/content/100/11/446/F2.large.jpg)

**FIGURE 2.** Changes in AH interval and AVCT as a function of recovery time before (CTL) and after (DRUG) intravenous administration of 25 mg/kg desethylamiodarone in a typical dog. Changes in AH interval and AVCT from minimum values (delta AH and delta AVCT) are expressed in milliseconds. Under control conditions, increases in AH interval were a log-linear function of recovery time. In the presence of amiodarone or desethylamiodarone, the relationship became biexponential, with a faster component having a time constant in the same range as control values and a slower component with a time constant in the range of 1 sec. The graphs show experimental points and lines of best fit using a monoexponential (CTL) or biexponential (DRUG) model. In experiments in which both AH and AVCT data were available, parallel changes in these variables were observed.
amiodarone did not produce any change from control in the relationship between $V_{max}$ and premature coupling interval.

Discussion

We have shown that the effects of amiodarone and its active desethyl metabolite on AV nodal properties are frequency dependent. At a heart rate of 60 beats/min, these agents increased AV conduction time and AVERP by an average of 25% and 31%, respectively (pooled data from all dogs). In contrast, at an atrial rate of 150 beats/min, AVCT was increased by a mean of 62% and AVERP by 85%. The magnitude of changes in AV nodal properties that we observed at slow heart rates is similar to changes measured by other investigators after administration of amiodarone in man.\textsuperscript{18, 19} No comparable clinical studies regarding amiodarone’s effect on the AV node at rapid heart rates are available. The frequency dependence of amiodarone’s actions on AV nodal conduction should be valuable in selectively suppressing reentrant tachycardias involving the AV node and reducing the ventricular response rate in atrial fibrillation.

The mechanisms underlying amiodarone’s frequency-dependent effect on AV conduction can, to large measure, be deduced from these observations. Under control conditions, the interval dependence of changes in AV conduction time was a monoexponential function of recovery interval. The time constant of this recovery process is in the same range as recovery time constants for slow inward current measured in vitro.\textsuperscript{20} In the presence of amiodarone or its metabolite, the AV recovery curve became biexponential, with a rapid phase having a time course similar to control and a slower phase with a time constant of 1 sec. This behav-

![FIGURE 3. Typical slow response action potentials recorded in the absence (top) and presence (bottom) of 5 \( \mu \)M amiodarone. The horizontal lines to the left of each action potential indicates the zero value, and the scale inset indicates 20 mV (vertical deflection) and 50 msec (horizontal deflection) for the action potential and 2 V/sec and 10 msec for the differentiated signal. Results are shown at a variety of basic cycle lengths (BCL), with amiodarone producing a frequency-dependent reduction in $V_{max}$ without otherwise significantly altering the action potential.](http://circ.ahajournals.org/)
ior is identical to that seen in the presence of the calcium-channel blockers verapamil, diltiazem, and nifedipine. It is most simply understood as the reflection of the recovery rates of drug-free and drug-bound calcium channels. Drug-free channels recover at a rate similar to the recovery of channels under control conditions, in the absence of drug. Drug-bound channels recover at a rate determined by the diastolic dissociation of the blocking drug from the channel receptor. The rate of diastolic unbinding is determined by the biophysical properties of the drug and is a characteristic of sodium- and calcium-channel blockers.

Further evidence for interval-dependent, slow channel-blocking properties of amiodarone is provided by our studies in vitro. Slow-channel action potentials produced by superfusion with elevated potassium concentrations and isoproterenol have been widely used as a tool to evaluate the effects of a variety of drugs on cardiac slow inward channels. Premature activation of our preparations in vitro under control conditions resulted in depression of \( V_{\text{max}} \), with a dependence on coupling interval similar to the time course of AVCT recovery in vivo. Amiodarone markedly slowed the recovery of \( V_{\text{max}} \). In two experiments, \( V_{\text{max}} \) recovery in the presence of amiodarone was biexponential, reflecting rapid recovery of drug-free channels and slower recovery of drug-bound channels. For five other experiments, only a slow recovery phase was observed, suggesting that extensive drug binding resulted in refractoriness before the recovery process of unbound channels was impinged upon. The time constant of the slow recovery phase was similar in all seven experiments and was of the same order as the slow-phase recovery time constant observed in the presence of amiodarone in vivo (table 2).

These observations provide strong evidence that amiodarone is a use-dependent, slow-channel blocker. Nishimura et al. have presented preliminary results indicating that amiodarone is a use-dependent \( \text{Ca}^{2+} \) current-blocker in voltage-clamped guinea pig ventricular cells. Calcium-sensitive effects of amiodarone on the function of perfused sinus and AV nodes in vitro are also compatible with a calcium channel–blocking action of the drug, as are the effects of amiodarone on \( ^{3}\text{H}-\text{nitrendipine binding to cardiac sarcolemma.} \)

Calcium channel–blocking properties of amiodarone could account for a variety of important clinical observations. The antianginal effects of amiodarone are consistent with calcium-channel blockade, as are the occasional adverse effects of hypotension and left ventricular dysfunction. Changes in sinoatrial and AV nodal function are also attributable to amiodarone’s calcium channel–blocking properties and account for beneficial effects against reentrant supraventricular tachycardias and atrial fibrillation as well as for the adverse consequences of sinus node dysfunction and AV block. Although amiodarone is perhaps best known for its ability to prolong the QT interval, it has rarely been implicated in the initiation of torsades de pointes arrhythmias associated with the long QT syndrome. Early afterdepolarizations are currently believed to be central in the pathogenesis of the ventricular tachyarrhythmias in the long QT syndrome. Recent work suggests that early afterdepolarizations are caused by a slow channel–dependent mechanism, implying that the rarity of amiodarone-induced long QT syndromes may be a result of amiodarone’s ability to depress the slow current responsible for arrhythmogenesis. Amiodarone has in fact been shown to depress depolarization-induced automatic-

**FIGURE 5.** Changes in \( V_{\text{max}} \) of slow-response action potentials as a function of recovery time before and after superfusion of amiodarone. Differences (d\( V_{\text{max}} \)) between steady-state \( V_{\text{max}} \) and \( V_{\text{max}} \) at each coupling interval are expressed in volts per second and plotted as a function of coupling interval. Before drug infusion there was a monoexponential relationship between changes in \( V_{\text{max}} \) and coupling interval, with a time constant of 79 msec. In the presence of amiodarone in this experiment, a biexponential relationship appeared, with time constants of 75 and 1750 msec. A similar slow phase of recovery was seen in all seven experiments; however, a quantifiable rapid recovery phase was seen in the presence of amiodarone in only two experiments. The lines of best fit to experimental data as determined by least-squares regression are shown.
ity; a membrane phenomenon with properties very similar to those of early afterdepolarizations.

The time course of recovery of slow-channel properties from amiodarone blockade is also significant. It is substantially more rapid than the recovery from blockade by verapamil and diltiazem, and considerable unbinding of amiodarone and its metabolite would be anticipated before the next activation at normal heart rates. This could account for the rarity of AV block and left ventricular dysfunction as adverse effects of amiodarone. On the other hand, at the rapid activation rates characteristic of atrial fibrillation and AV reentrant tachycardias, the diastolic time available for drug unbinding between AV nodal activations is substantially less than amiodarone’s recovery time constant. Consequently, block would be expected to accumulate and AV nodal conduction would be depressed. The ideal recovery time constant to allow for depression of tachycardias with little effect during sinus rhythm is in the range of 0.5 to 1 sec. In this study, amiodarone’s effects on slow-channel properties were found to recover with a time constant in this theoretically optimal range.

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