Effects of Flecainide and Quinidine on Human Atrial Action Potentials
Role of Rate-Dependence and Comparison With Guinea Pig, Rabbit, and Dog Tissues

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Flecainide and other class IC antiarrhythmic drugs are effective in the prevention and termination of atrial fibrillation, but the mechanism of this action is unknown. To gain insights into potential cellular mechanisms, we evaluated the response of human atrial action potentials to equimolar therapeutic concentrations of flecainide and quinidine and compared this response to that of guinea pig, rabbit, and dog atria. Both compounds reduced $V_{\text{max}}$ more as activation rate increased, but flecainide was more potent than quinidine and had slower kinetics. The rate-dependence of $V_{\text{max}}$ reduction was similar for all species, but human tissue was more sensitive to the drugs tested. In contrast to changes in $V_{\text{max}}$, drug-induced alterations in action potential duration showed opposite rate-dependence for the two drugs. Quinidine increased action potential duration to 95% repolarization (APD$_{95}$) in human atria by 33±7% (mean±SD) at a cycle length of 1,000 msec, but this effect was reduced as cycle length decreased, to 12±4% ($p<0.001$) at a cycle length of 300 msec. Flecainide increased APD$_{95}$ (by 6±3%) much less than quinidine at a cycle length of 1,000 msec, but its effect was increased by faster pacing, to 27±12% at a cycle length of 300 msec and 35±8% ($p<0.001$) at the shortest 1:1 cycle length. The rate-dependent response of APD to drugs was qualitatively similar but quantitatively different among species. Human tissue showed the greatest frequency-dependent drug effects on repolarization, followed by tissue from dogs and rabbits. Guinea pig atria showed the least (and statistically nonsignificant) rate-dependence of drug effect on APD. Drug-induced changes in refractoriness paralleled those in APD. We conclude that: 1) flecainide and quinidine both increase APD in human atrial tissue but with opposite rate-dependence, 2) the effects of flecainide to increase atrial APD and refractoriness are enhanced by the rapid rates typical of atrial fibrillation, and 3) animal tissues may differ importantly from human in both their sensitivity and rate-dependent response to antiarrhythmic drugs. The salutary response of atrial fibrillation to flecainide may be due to enhancement of drug action by the rapid atrial activation rates characteristic of this arrhythmia. (Circulation 1990;82:274–283)

Class IC drugs characteristically slow conduction without significantly altering refractory period. Because slow conduction is an important predisposing factor to reentry, these properties of IC agents would not be expected to confer beneficial actions against reentrant arrhythmias. Atrial fibrillation has long been considered a reentrant arrhythmia. The original “multiple wavelet reentry” concept of Moe et al has been confirmed by recent experimental work in both animals and humans. Recently, there has been increasing awareness of the value of class IC drugs in the prevention and termination of atrial fibrillation. Propafenone and flecainide prevent recurrences of paroxysmal atrial fibrillation and furthermore, flecainide is effective in cardioverting atrial fibrillation, particularly of recent onset. The ability of flecainide to stop atrial fibrillation is similar to that of quinidine and greater than that of verapamil. Flecainide reduces the recurrence rate of atrial fibrillation after electrical cardioversion more effectively than disopyramide.
The ability of class IC agents to terminate and prevent atrial fibrillation is difficult to understand in the light of classical determinants of reentry and the typical actions of this class of drugs. Thus, either our concepts of the determinants of reentry are erroneous, or our understanding of the actions of IC agents is inaccurate. Because ideas about reentry are supported by much experimental evidence, we chose to consider in more detail the electrophysiologic actions of class IC compounds. Specifically, we wanted to study in depth the effects of a class IC compound on atrial action potential duration (APD) and refractoriness to assess whether such effects might account for its beneficial actions against atrial fibrillation.

Three variables have not been carefully considered in evaluating IC drug effects on refractoriness: tissue type, species, and heart rate. Most in vitro studies of IC drug action have used ventricular muscle and Purkinje fiber preparations. Very limited data are available regarding IC drug effects on atrial action potentials.20,21 Because the characteristics of atrial action potentials differ from those of ventricular muscle or Purkinje fibers,22 ideas based on observations in the latter tissues may not apply to IC effects on atria. Furthermore, it is known that the properties and ionic determinants of APD may differ greatly, even for the same type of tissue, among different animal species.23–27 To understand the potential mechanisms of IC drug actions on atrial arrhythmias in humans, it is important to know the effects of IC compounds on human atrial tissues, or at least on the tissues of animal atria known to respond similarly to those in humans. Finally, heart rate is known to be an important modulator of drug effects on repolarization.28–30 It is conceivable that a drug would have little effect on atrial APD and refractoriness at a normal heart rate while substantially increasing these variables at the rapid rates characteristic of atrial fibrillation.

The present experiments were designed to clarify some of these issues. We chose flecainide as the prototype class IC drug for study because it has been the IC agent most extensively evaluated in the treatment of atrial fibrillation.10–19 Quinidine was chosen as a reference class IA compound because of its widespread and longstanding use in the treatment of atrial fibrillation.31 We compared the effects of flecainide with those of quinidine on atrial action potentials as a function of activation rate, using tissue from patients undergoing coronary artery bypass surgery, as well as from three animal species (guinea pigs, rabbits, and dogs).

**Methods**

**Preparations**

Atrial muscle strips were obtained from guinea pigs, rabbits, dogs, and humans. Adult guinea pigs of either sex weighing about 350 g were killed by decapitation. Their hearts were rapidly removed, washed in cool, oxygenated Tyrode’s solution, and the atrial muscle was dissected free. New Zealand rabbits of either sex weighing about 2 kg were anesthetized (sodium pentobarbital, 20 mg/kg i.v.), and their hearts were quickly removed through a subcostal incision. Dog atrial strips were isolated from hearts removed via a right thoracotomy from anesthetized (sodium pentobarbital, 30 mg/kg i.v.) mongrel dogs of either sex weighing 15–20 kg.

Human tissues consisted of small pieces from the apex of the right atrial appendage obtained during coronary artery bypass surgery. The patients (n=12) ranged in age from 45 to 73 (mean, 58) years, and included 11 men and one woman. All patients had normal P waves on electrocardiography, and no patient had a history of supraventricular arrhythmias. No patient had evidence of atrial enlargement or congestive heart failure on chest radiograph, and all but one patient had normal left ventricular function. The patient with abnormal left ventricular function had an ejection fraction of 48% and moderate mitral regurgitation. No other patients had mitral valve disease. The only medications taken by these patients were for the treatment of angina and, in one case, enalapril for hypertension. No patients were taking digitalis or antiarrhythmic drugs. All atrial specimens were grossly normal at the time of excision. Immediately after excision, samples were immersed in oxygenated Tyrode’s solution maintained at 10–15°C and brought to the laboratory. The time between excision and the beginning of laboratory processing was about 15 minutes. The dissection procedure was performed in a chamber containing oxygenated Tyrode’s solution at room temperature.

Preparations obtained by the above procedures were pinned to the Sylgard-covered bottom of a 20-ml Lucite chamber with the endocardial surface facing upward and were superfused with Tyrode’s solution at 8 ml/min. The superfusion solution contained (mM): NaCl 116, NaHCO3 18, dextrose 10, KCl 4, NaH2PO4 0.9, MgCl2 0.5, and CaCl2 1. The superfusate was aerated with 95% O2-5% CO2, and the bath temperature was maintained at 36°C by a heating element and proportional power supply (Hanna Instruments, Philadelphia, Pennsylvania). One hour was allowed for tissue equilibration before experiments were begun. A total of 17 preparations of guinea pig atrium were studied, compared with 20 for rabbits, 17 for dogs, and 15 obtained from patient samples. Two preparations for study could be obtained from some human atrial samples, allowing us to compare the effects of both drugs in tissues from the same heart.

**Microelectrode Techniques**

Glass microelectrodes filled with 3 M KCl and with tip resistances of 8–20 MΩ were coupled by a silver–silver chloride junction to a high-impedance microelectrode amplifier (WPI KS-700, World Precision Instruments, New Haven, Connecticut). A bipolar Teflon-coated platinum electrode was used to deliver square-wave pulses of 2-msec duration and
twice late diastolic threshold current to stimulate the preparation. A programmable stimulator and stimulus isolation unit (Bloom Instruments, Flying Hills, Pennsylvania) were used to deliver stimuli with selected stimulation paradigms.

Signals were displayed on a storage oscilloscope (Tektronix 5115, Tektronix Inc., Beaverton, Oregon) and were converted into digital form using a Tekmar 100-kHz A/D converter (Tekmar Co., Cincinnati, Ohio). The differentiated signal was displayed on the oscilloscope, and the maximum amplitude of the signal was transmitted via a peak hold unit into the A/D converter. Custom-made software routines (Bascom Consultants, Montreal, Quebec, Canada) and an IBM PC computer were used to measure action potential characteristics.

Experimental Protocol

Action potential characteristics, including resting potential, action potential amplitude, APD to 50% and 95% repolarization (APD50 and APD95, respectively), and maximum rate of voltage rise during phase 0 (Vmax), were determined at basic cycle lengths of 1,000, 600, 300, and 150 msec, respectively. In human tissues, 1:1 capture was generally unattainable at a cycle length of 150 msec. The shortest pacing interval attainable averaged 180 msec under control conditions and was increased 34% by flecainide (p < 0.001) and 24% by quinidine (p < 0.001). At each cycle length, 5 minutes was allowed for action potential characteristics to reach a steady state before measurements were made. Effective refractory period (ERP) was measured by the extrastimulus technique. A premature stimulus of twice diastolic threshold current was introduced after each train of eight basic beats. Coupling interval was reduced gradually until failure to capture occurred, defining the ERP. Diastolic threshold current was verified at each cycle length, and the stimulus strength was adjusted accordingly. All ERP determinations were performed in duplicate to ensure reproducibility. After measurements were made under control conditions, the test drug was added to the superfusate, and action potential characteristics were monitored over time. The measurements made under control conditions were repeated after 30 minutes of drug superfusion and after 30 minutes of washout. Continuous stable impairment of the same cell under both control and drug conditions was required for all analyzed experiments. In some experiments, when drug effects disappeared completely at washout and the impairment remained stable, the alternative agent was studied in the same preparation. When this was not possible, an attempt was made to study both drugs in tissues from the same animal.

Equimolar concentrations (4.5 μM) of flecainide and quinidine were used in guinea pig, rabbit, and dog, corresponding to 1.8 mg/l flecainide and 1.4 mg/l quinidine. Human tissues were found to be more sensitive to the effects of flecainide than atria from the other species studied, so we reduced the flecainide and quinidine concentrations by 50%, to 2.25 μM, in studies of human atria. The resulting concentrations, 0.9 mg/l of flecainide and 0.7 mg/l of quinidine, are in the therapeutic range of free plasma drug concentration for either compound. Flecainide acetate was obtained from Riker Laboratories, Inc. (St. Paul, Minnesota), and quinidine gluconate was supplied by Rougier-Desbiens, Inc. (Montreal, Canada). Both compounds were dissolved in Tyrode’s solution at the molar concentrations noted above, using the formula weight of the salt to calculate the amount of each compound necessary.

Statistical Analysis

Group data are presented as mean ± SD. A logarithmic transformation was used for statistical analysis of data that were not normally distributed. The rate-dependence of drug action was evaluated by analysis of variance (ANOVA) with an F test for interaction. Multiple comparisons data were evaluated by ANOVA with Scheffe contrasts. A two-tailed probability of ± 5% was taken to indicate statistical significance. Linear regression analysis was performed using the least sum of squares method.

Results

Action Potential Characteristics in Atrial Tissues From Different Species

Representative atrial action potentials recorded from different species under control conditions at a cycle length of 1,000 msec are illustrated in Figure 1, and mean action potential characteristics at the same cycle length are summarized in Table 1. Action potentials of various species differed from each other qualitatively and quantitatively.

Indexes reflecting net phase 0 inward current, such as action potential amplitude, overshoot, and Vmax were smaller in human and rabbit tissues than in guinea pig or dog (Table 1). Initial repolarization was faster in rabbit tissues, as reflected by a short APD90 and in human tissues, causing a consistent “spike and dome morphology” (Figure 1), than in guinea pigs or dogs. Total APD was comparable in rabbits and guinea pigs, was greater in dogs, and was greater still in humans. ERP values generally paralleled those of APD95.

Rate increases did not alter the appearance of canine or guinea pig action potentials but decreased their duration. Rabbit tissues responded to increased rate with the appearance of a distinct plateau, in contrast to the triangular action potentials at a cycle length of 1 second. In human tissue, rapid pacing resulted in a loss of the characteristic spike and dome seen at cycle lengths greater than 500 msec.

Effects of Flecainide and Quinidine on Atrial Action Potential Characteristics

Both drugs significantly increased APD and refractory period while reducing Vmax and action potential amplitude. Drug-induced changes in Vmax were of the
same approximate magnitude in all species tested (Figure 2). Because human tissues were exposed to half the concentration used for other species, however, the sensitivity of human atrium to these compounds was greater than that of the other species tested. The effects of both compounds on $V_{\text{max}}$ were rate-dependent, with greater depression occurring at shorter cycle lengths.

### Table 1. Action Potential Characteristics Recorded From Atrial Tissues of Different Species at a Cycle Length of 1,000 msec

<table>
<thead>
<tr>
<th>Species</th>
<th>Guinea Pig</th>
<th>Rabbit</th>
<th>Dog</th>
<th>Human</th>
</tr>
</thead>
<tbody>
<tr>
<td>$R_P$ (mV)</td>
<td>76±4</td>
<td>81±5</td>
<td>76±3</td>
<td>80±3</td>
</tr>
<tr>
<td>$A_P$ (mV)</td>
<td>113±6</td>
<td>99±9</td>
<td>106±8</td>
<td>98±5</td>
</tr>
<tr>
<td>$O_S$ (mV)</td>
<td>35±7</td>
<td>20±5</td>
<td>31±4</td>
<td>18±4</td>
</tr>
<tr>
<td>$A_PD_{50}$ (msec)</td>
<td>52±7</td>
<td>20±4</td>
<td>84±10</td>
<td></td>
</tr>
<tr>
<td>$A_PD_{95}$ (msec)</td>
<td>120±13</td>
<td>101±13</td>
<td>205±14</td>
<td>364±59</td>
</tr>
<tr>
<td>$V_{\text{max}}$ (V/sec)</td>
<td>219±35</td>
<td>167±30</td>
<td>206±24</td>
<td>167±26</td>
</tr>
<tr>
<td>$E_R$ (msec)</td>
<td>82±7</td>
<td>87±12</td>
<td>180±15</td>
<td>324±59</td>
</tr>
</tbody>
</table>

$R_P$, resting potential; $A_P$, action potential amplitude; $O_S$, overshoot; $A_PD_{50}$, $A_PD_{95}$, action potential duration to 50% and 95% of repolarization, respectively; $V_{\text{max}}$, maximum rate of phase 0 voltage rise; $E_R$, effective refractory period.

Results shown are from 17 preparations for guinea pig, 20 for rabbit, 17 for dog, and 15 for human.

$p<0.01$, $p<0.001$, $p<0.0001$ for comparison indicated by analysis of variance with Scheffe's test.

$A_PD_{50}$ data not shown for human tissue because action potentials frequently crossed 50% repolarization value twice.
The magnitude and rate-dependence of changes in APD were more variable between species (Figure 3) than those in $V_{\text{max}}$. Human tissues were the most sensitive to the effects of both compounds. Changes in APD showed significant rate-dependence for both compounds in rabbit, dog, and human atria. No significant rate-dependence was noted for either drug's effect on APD in guinea pigs. There was a striking difference in the direction of rate-dependent effects on APD between compounds. Whereas quinidine's actions were reduced as cycle length decreased, the opposite was true for flecainide: rapid pacing greatly increased the latter's effects on repolarization. These differences were most striking in human tissue. Quinidine increased APD$_{95}$ by 33±7% at a cycle length of 1 second (rate, 60 per minute), a much greater increase than the 6±3% change produced by flecainide at the same rate. On the other hand, at a cycle length of 300 msec (200 per minute), the effect of quinidine was reduced to a 12±4% increase, whereas flecainide increased APD$_{95}$ by 27±12%. These effects were paralleled by changes in ERP (Figure 4). In human tissue, quinidine increased ERP by 37±9% at a rate of 60 per minute compared with an 8±3% increase by flecainide. In contrast, at the fastest pacing rate with 1:1 capture, quinidine increased ERP by 23±4% compared with a 40±6% increase caused by flecainide.

Figure 5 illustrates the effects of both compounds in the same canine preparation. Under control conditions, decreasing the cycle length from 1,000 to 150 msec resulted in substantial shortening of APD. Flecainide attenuated the rate-dependent APD shortening, resulting in a maximal drug-induced APD increase at the shortest cycle length. In the presence of quinidine, however, APD accommodation to changes in frequency was enhanced. This led to maximum changes at long pacing cycle lengths, with effects attenuated by rapid pacing. Drug-induced changes in APD accommodation were even more pronounced in human tissues. Figure 6 shows typical effects of flecainide (top) and quinidine (bottom) in a representative human atrial preparation for each. Under control conditions, decreases in cycle length produce substantial APD reductions (note that the time base is twice as slow as for dog tissue in Figure 5). Flecainide virtually eliminated APD accommodation to rate change in this and all other human atrial preparations, whereas quinidine consistently increased the amount of APD change in response to APD alteration.
Figure 5. Effects of flecainide and quinidine on action potential characteristics of representative canine atrial preparation. Action potential duration (APD) and $V_{\text{max}}$ decreased as basic cycle length was reduced from 1,000 to 600, 300, and 150 msec under control conditions (top left), and in the presence of flecainide (bottom left) and quinidine (bottom right). The degree of APD change with changing rate was reduced by flecainide and increased by quinidine. Continuous impalement of the same cell was maintained under control conditions, superfusion of flecainide, washout back to control, and superfusion with quinidine. Vertical scale represents 20 mV for action potential and 100 V/s for differentiated signal.

Quantitative Analysis of Rate-Dependent Effects of Flecainide and Quinidine

To quantify the rate-dependence of drug effects on $V_{\text{max}}$ in different species, we used an approach developed theoretically by Starner.34 When the inverse of drug-induced blockade (reflected by changes in $V_{\text{max}}$) is plotted against basic cycle length, a linear relation should result, with a slope proportional to the rate constant of drug action.34 Figure 7 shows representative results from one experiment in each species with each compound. As predicted, the relations were linear in all experiments. The slopes for each compound were similar across the various species studied, but the slopes for flecainide were consistently less than those for quinidine. Table 2 shows mean rate constants as determined by this approach. There were no significant differences in rate constants for a given drug among different species, but the rate constant for flecainide was consistently less than that for quinidine.

Rate-dependent effects on APD were also analyzed quantitatively. Drug-induced increases in APD were plotted as a function of cycle length in each experiment, and the slope of the resulting relation was calculated. Whereas the absolute value of slopes opened theoretically by Starner,34 the rate constant for block should be proportional to the slope of a plot of the inverse of blockade at each cycle length versus the basic cycle length (BCL). We therefore plotted the inverse of drug-induced changes in $V_{\text{max}}$ (calculated as change from control divided by control value) at each BCL vs. BCL in each experiment. The data fell along a straight line, as predicted by Starner. Slopes of resulting lines were steeper for quinidine than for flecainide, indicating a greater rate constant, and were not significantly affected by species.

Table 2. Frequency-Dependent Effects of Flecainide and Quinidine: Dependence of $V_{\text{max}}$ Changes on Cycle Length

<table>
<thead>
<tr>
<th>Rate constant*</th>
<th>Guinea pig</th>
<th>Rabbit</th>
<th>Dog</th>
<th>Human</th>
</tr>
</thead>
<tbody>
<tr>
<td>Flecainide</td>
<td>3.6±0.9</td>
<td>2.6±1.7</td>
<td>1.9±0.4</td>
<td>1.9±0.6</td>
</tr>
<tr>
<td>Quinidine</td>
<td>16.2±8.2†</td>
<td>10.1±8.4</td>
<td>7.1±3.1‡</td>
<td>7.6±2.9§</td>
</tr>
</tbody>
</table>

*Rate constant shown is the slope of data plotted as shown in Figure 7, and is proportional to the rate constant for sodium channel blockade.

†p<0.01; ‡p<0.05 for differences between flecainide and quinidine.
Table 3. Frequency-Dependent Effects of Flecainide and Quinidine: Dependence of APD<sub>95</sub> Changes on Cycle Length

<table>
<thead>
<tr>
<th></th>
<th>Guinea pig</th>
<th>Rabbit</th>
<th>Dog</th>
<th>Human</th>
</tr>
</thead>
<tbody>
<tr>
<td>Flecainide</td>
<td>-13.2±4.7t</td>
<td>-15.3±3.3†</td>
<td>-20.3±6.4</td>
<td>-23.5±9.0</td>
</tr>
<tr>
<td>Quinidine</td>
<td>6.9±19.6††</td>
<td>15.6±5.1††</td>
<td>15.1±2.9††</td>
<td>27.4±4.1††</td>
</tr>
</tbody>
</table>

*<i>p</i>&lt;0.05; †<i>p</i>&lt;0.001 for difference between flecainide and quinidine; ‡<i>p</i>&lt;0.05 compared with slope in human atrium.

were similar for quinidine compared with flecainide, slopes for quinidine were consistently positive (indicating increasing effect with increasing cycle length) and those for flecainide were negative. Consequently, the slopes of APD change were significantly different between drugs in all species (Table 3). The rate-dependence of APD change was greatest in human tissues. The slope of APD change versus cycle length was significantly larger in human atria than in guinea pig and rabbit tissues for flecainide, and greater than in all other species for quinidine.

**Discussion**

The efficacy of class IC drugs in treating atrial fibrillation is clear, and yet the mechanism of this action has been unexplained. Our results suggest that consideration of the role of atrial activation rate and species-dependent differences in drug response may be important in understanding IC effects in atrial fibrillation.

**Role of Rate-Dependent Drug Actions**

Both flecainide and quinidine reduced $V_{\text{max}}$ in a frequency-dependent way. The kinetic rate constant for quinidine was approximately four times as large as that for flecainide, a relation similar to that provided by direct measurements in the literature. There were no significant differences in rate constants for a given drug among species. On the other hand, quinidine and flecainide effects on APD showed opposite rate-dependence, and the rate-dependence of drug action in human tissues was significantly more than in other species. The effects of flecainide on ERP were similarly rate-related. Whereas it would be fair to say that, as is commonly assumed, flecainide has little effect on atrial refractoriness at rates similar to resting sinus rhythm in humans, rapid rates greatly enhance flecainide-induced ERP prolongations. At rates comparable to that of the fibrillating atrium, flecainide had a substantially greater effect on atrial ERP than did quinidine. Moe et al<sup>35</sup> pointed out the critical importance of atrial refractoriness in controlling the occurrence of fibrillation in their computer model. More recently, Feld et al<sup>36,37</sup> have established the importance of changes in atrial refractoriness in determining drug effects in an experimental model of atrial flutter. These results imply that rate-dependent increases in ERP may play a central role in the atrial antifibrillatory actions of flecainide.

**Species Specificity of Response**

Consistent differences were seen in control atrial action potentials among the species studied. The rapid phase 1 repolarization typical of human and rabbit atria is consistent with the large transient outward current present in these tissues. The transient outward current activates and inactivates rapidly and then recovers from inactivation with a slower time course. This may result in a “spike and dome” morphology, as we consistently observed in human atria. The rapid activation of this outward current may explain the smaller values for action potential amplitude, $V_{\text{max}}$, and overshoot in human and rabbit atrial action potentials compared with those from dog.

There have been few comparative studies of the drug response of tissues from various animal species. Our results show that, at least for atrial tissues, there are important species differences in the response to antiarrhythmic drugs. We had to use twice the concentration of flecainide and quinidine in guinea pig, rabbits, and dogs compared with humans to achieve a pharmacologic response in a similar range. Even at a smaller dose, the effect of quinidine was greater in human tissues than for the other species studied. These results are consistent with previous observations of a requirement for larger plasma drug concentrations in dogs to achieve electrophysiologic effects comparable to those of therapeutic concentrations in humans. Furthermore, the rate-dependence of drug-induced repolarization changes also varied among species. The response of guinea pig atrial APD to quinidine and flecainide showed the least rate-dependence, whereas that of human tissue showed the most sensitivity to activation rate. Although the overall pattern of rate-dependent action was similar for all species, its magnitude was not.

Our results bear on both the value and limitations of the pharmacologic response of animal tissues as an indicator of drug effects in humans. Although the responses were qualitatively similar in different species, quantitative differences in sensitivity and in the magnitude of rate-dependence make extrapolation to humans uncertain. The responses of canine atria were most similar to those of humans, and the responses of guinea pig tissues, the least similar, but certainly none were identical.

**Mechanisms of Rate- and Species-Dependent Action**

Rate-dependent drug effects on $V_{\text{max}}$ are caused by preferential drug binding to sodium channels in the open or inactivated state, followed by time-dependent unbinding after repolarization. We found that the rate-dependence of $V_{\text{max}}$ blockade by flecainide and quinidine was not substantially affected by species. Previous kinetic studies of $V_{\text{max}}$ depression by lidocaine in guinea pig papillary muscles and canine and sheep Purkinje fibers have shown similar time constants. No species dependence of the kinetics of sodium channel
blockade has been found for other drugs tested. Although the kinetics of drug action on $V_{\text{max}}$ seemed to be species-independent, the magnitude of depression of $V_{\text{max}}$ differed among the species tested. Human tissue was the most sensitive, with canine intermediate, and rabbit and guinea pig the least sensitive. These differences in sensitivity may have been partially due to differences in APD, which is longest in humans, intermediate in dogs, and shortest in rabbits and guinea pigs. Inactivated state block occurs predominantly during the plateau and is therefore enhanced by longer action potentials.

A variety of mechanisms may play a role in rate-dependent drug effects on APD. The kinetics of activation and inactivation of target plateau currents may be very important. For example, the transient outward current is a major repolarizing current in rabbit and human atrial tissue, and is inactivated at rapid rates. Quinidine blocks transient outward current, and this effect would be expected to be most important when the current is large (i.e., slow rates) and least important when the current is small (fast rates). This property would result in APD prolongation by quinidine predominantly at slow rates, as we observed. Flecainide would have to block a current with different kinetics to explain its enhanced action on APD at rapid rates. Alternatively, rate-related drug effects on APD could be due to state-dependent interactions of antiarrhythmic drugs with potassium channels. Roden et al. have proposed that quinidine promotes occupancy of a closed state of the delayed rectifier, perhaps by associating preferentially with closed channels. Bradycardia-dependent APD prolongation by quinidine would result from a longer closed-state cycle, whereas tachycardia-dependent APD prolongation (of the type we showed for flecainide) would result from preferential binding to the open state. Definitive identification of the mechanisms underlying rate-dependent APD changes awaits detailed voltage-clamp studies of drug effects on atrial plateau currents.

Relation to Previous Studies in the Literature

The resting potential of our human atrial samples (mean, $-80$ mV) was in the same range as values obtained by Gelband et al. ($-86$ mV) and Mary-Rabine et al. ($-78$ mV) in normal atrial tissues. Lower values are observed in patients with diseased atria. The morphology of our human atrial action potentials had a prominent spike and dome, like the cells termed “atrial specialized fibers” by Gelband et al. Many previous reports of human atrial action potentials are from studies using tissue samples from a pediatric population, in which two forms of atrial action potential are seen. The action potential morphology of our human atrial tissues was similar to the morphology uniformly observed in adult atrial fibers by Escande et al, who found that the development of the adult action potential morphology coincided with the appearance of a large transient outward current.

Quinidine has been shown to increase APD in guinea pig, rabbit, and canine atrial tissues. We are not aware of in vitro studies of the actions of quinidine on human atrial tissue. West and Amory found, as we did, that increased driving rate reduces the effects of quinidine on canine atrial APD.

Ikeda et al. reported that 1 mg/l flecainide increased APD in rabbit atria by $12.8\%$ at an unspecified frequency. This value is similar to the changes we observed at cycle lengths between 300 and 1,000 msec. Le Grand et al. have reported preliminary findings of flecainide-induced increases in human atrial refractoriness in vitro that are enhanced by increased driving rate. They noted rate-dependent increases in APD but not in APD. This apparent discrepancy with our findings is difficult to assess because their results are reported only in abstract form. The only other observation of class IC drug effects on atrial tissue that we could find was a study showing that encainide increases atrial monophasic APD in dogs. The role of heart rate as a potential modulator of drug action was not examined.

Potential Limitations

Any study evaluating tissue obtained from patients with heart disease must consider the possibility of abnormalities in the tissue samples. We excluded patients with a history of atrial arrhythmias or electrocardiographic evidence of atrial disease, and all tissue samples appeared grossly normal. The baseline values of atrial ERP that we measured using human tissues in vitro (ERP of 276±38 msec at a cycle length of 600 msec) are in the same range as values previously reported during electrophysiologic study.

Significance of These Findings

These findings have implications both for the specific actions of class IC drugs on atrial tissues and for the general approach to understanding the clinical effects of antiarrhythmic drugs. Microelectrode studies of antiarrhythmic drug action on tissues isolated from experimental animals have provided many potential insights into the mechanisms of clinical drug action. On the other hand, we have found that there are important differences between the response of atrial tissues from various animal species. Human tissues appear to be more sensitive to the effects of quinidine and flecainide, a finding compatible with previous in vivo and in vitro observations with other compounds. Although the rate-dependence of $V_{\text{max}}$ depression was not species-dependent, the dependence of repolarization changes on frequency varied widely among the species studied. Had our experiments been conducted only on guinea pig atria, we would have concluded that quinidine- and flecainide-induced changes in atrial APD are not rate-dependent, a conclusion that would not apply to other species. Extrapolation from observations in other species to humans must therefore be very considered and requires confirmation either by direct observations in isolated human tissue.
samples or by evaluation of electrophysiologic properties in the clinical electrophysiology laboratory. These findings may be relevant for understanding the beneficial actions of flecainide in the treatment of atrial fibrillation. Furthermore, they indicate a potentially desirable antiarrhythmic drug property meriting further investigation. Drugs that increase ERP without altering conduction are the ideal agents with which to treat reentrant arrhythmias. Whereas class III agents have such properties, their use is complicated by the possible occurrence of the acquired long QT syndrome. The potentially lethal ventricular tachyarrhythmias that result are thought to be a consequence of early afterdepolarizations attendant on marked action potential prolongation at slow heart rates. If drugs could be developed that delayed repolarization and prolonged refractoriness selectively at the rapid rates characteristic of clinical tachyarrhythmias, they could prevent the latter without the potential for causing a long QT syndrome. Flecainide appears to have such an action on repolarization, at least on atrial tissues, but its conduction-slowing properties limit its efficacy for reentrant arrhythmias. If other compounds could be developed that preferentially increase refractoriness at rapid rates without altering conduction, a clinically important advance might result.

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