Kinetics of Use-Dependent Ventricular Conduction Slowing by Antiarrhythmic Drugs in Humans

Suzanne Ranger, BSc; Mario Talajic, MD; Robert Lemery, MD; Denis Roy, MD; Christine Villemaire, BSc; and Stanley Nattel, MD

Background. Rate-dependent conduction slowing by class I antiarrhythmic agents has clinically important consequences. Class I drugs are known to produce use-dependent sodium channel blockade. If rate-dependent conduction slowing by class I agents is due to sodium channel blocking actions, the kinetics of conduction slowing should be similar to those of depression of sodium current indexes in vitro. The purpose of the present investigation was to study the onset time course of ventricular conduction slowing caused by a variety of class I agents in humans.

Methods and Results. Twenty-seven patients undergoing electrophysiological evaluation for antiarrhythmic therapy were studied. Changes in QRS duration at initiation of ventricular pacing at cycle lengths of 400 and 500 msec were used to evaluate the kinetics of drug action. Mean time constants for each drug were similar to values for Vmax, depression reported in vitro studies: flecainide, 24.9±11.6 beats in eight patients (versus 34.5 beats reported for Vmax block); propafenone, 17.8±6.9 beats in five patients (versus 8.4-20.8 beats); quinidine, 7.0±2.4 beats in six patients (versus 5.6-6.2 beats); and amiodarone, 3.6±2.0 beats for eight patients (versus 3.0 beats). Time constants were significantly different among the various drugs tested (p=0.0002 at a cycle length of 400 msec; p=0.002 at 500 msec), and there was a strong correlation (r=0.89, p<0.0001) between values obtained at a cycle length of 400 msec and those at a cycle length of 500 msec. No rate-dependent changes in QRS duration were seen at onset of ventricular pacing among eight age- and disease-matched control patients not taking class I antiarrhythmic drugs, including three patients subsequently showing such changes during type I antiarrhythmic drug therapy.

Conclusions. We conclude that class I agents produce use-dependent QRS prolongation in humans with characteristic kinetics for each agent that are similar to the kinetics of Vmax depression in vitro. These results suggest that rate-dependent ventricular conduction slowing by antiarrhythmic drugs in humans is due to use-dependent sodium channel blockade. 


Sodium channel blocking drugs are commonly used for the treatment of cardiac arrhythmias. Conduction slowing by these agents in humans has been found to depend on heart rate.1,2

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These observations are consistent with fundamental models of antiarrhythmic drug interaction with cardiac sodium channels.3,4 According to these models, depolarization, which results in channel opening and then inactivation, tends to facilitate drug binding to the sodium channel, whereas repolarization, which returns sodium channels to their resting state, tends to facilitate drug dissociation. Increases in cardiac rate enhance drug action by increasing the amount of time in the activated and inactivated states at the expense of time in the resting state.

Models of use-dependent channel blockade have important implications for mechanisms of clinical drug action.5,6 Rate-dependent blockade may contribute to the beneficial antiarrhythmic actions of both calcium7,8 and sodium9 channel blockers. In
other instances, rate-dependent blockade may result in proarrhythmic properties.10-12

A characteristic feature of use-dependent channel blockade is that it develops and dissipates with a typical time course for each antiarrhythmic agent.3-5 Studies in experimental animals have shown that the kinetics of conduction slowing due to both sodium10,13-18 and calcium19 channel blockers parallel their actions on \( V_{\text{max}} \) or inward current in vitro. We have shown that the onset of additional QRS prolongation upon an abrupt increase in ventricular rate in patients taking flecainide parallels the time dependence of flecainide’s effects on \( V_{\text{max}} \) in vitro.12 To our knowledge, this is the only quantitative study of the kinetics of use-dependent conduction slowing by an antiarrhythmic drug in humans. The possibility remains that the response we observed in the presence of flecainide was due to a nonspecific rate-dependent phenomenon such as myocardial ischemia, ion accumulation or depletion, and so on, and that the similarity to flecainide’s in vitro blocking kinetics is purely coincidental.

The latter possibility could be critically assessed by evaluating the time course of conduction slowing upon an abrupt rate change in the presence of a variety of antiarrhythmic drugs with different kinetics of sodium channel blockade in vitro. If a specific use-dependent blocking action is responsible for conduction slowing, a characteristic time course should be observed for each agent. If, instead, a nonspecific mechanism is responsible for conduction slowing, the time course of the latter should be constant irrespective of the drug studied. The present study was designed to determine whether abrupt increases in heart rate result in ventricular conduction slowing in the presence of a variety of class I antiarrhythmic drugs and to establish the time course of any changes seen. Preliminary results have been presented in abstract form.20

Table 1. Characteristics of Patient Population

<table>
<thead>
<tr>
<th>Drug</th>
<th>Flecainide</th>
<th>Propafenone</th>
<th>Quinidine</th>
<th>Amiodarone</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>8</td>
<td>5</td>
<td>6</td>
<td>8</td>
<td>8</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>59±10</td>
<td>63±14</td>
<td>56±12</td>
<td>57±9</td>
<td>64±10</td>
</tr>
<tr>
<td>Sex (male/female)</td>
<td>8/0</td>
<td>3/2</td>
<td>5/1</td>
<td>8/0</td>
<td>6/2</td>
</tr>
<tr>
<td>Cardiac diagnosis</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>8</td>
<td>3</td>
<td>6</td>
<td>8</td>
<td>6</td>
</tr>
<tr>
<td>Valvular</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No known cardiac disease</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td>2</td>
</tr>
<tr>
<td>Dosage (mg/day)</td>
<td>225±104</td>
<td>555±146</td>
<td>790±253</td>
<td>925±512</td>
<td>NA</td>
</tr>
<tr>
<td>Plasma concentration (( \mu \text{mol/l} ))</td>
<td>1.2±0.4</td>
<td>0.8±0.3*</td>
<td>8.0±4.4</td>
<td>2.0±0.6*</td>
<td>NA</td>
</tr>
<tr>
<td>Plasma concentration (mg/l)</td>
<td>0.5±0.2</td>
<td>0.3±0.1</td>
<td>2.6±1.4</td>
<td>1.25±0.4</td>
<td>NA</td>
</tr>
<tr>
<td>Ejection fraction (%)</td>
<td>35±9</td>
<td>37±9</td>
<td>33±8</td>
<td>25±9</td>
<td>41±14</td>
</tr>
<tr>
<td>Medication</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Digitalis</td>
<td>3/8</td>
<td>3/5</td>
<td>1/6</td>
<td>3/8</td>
<td>2/8</td>
</tr>
<tr>
<td>( \beta )-Blocker</td>
<td>1/8</td>
<td>0/5</td>
<td>1/6</td>
<td>1/8</td>
<td>2/8</td>
</tr>
<tr>
<td>Drug efficacy</td>
<td>2/8</td>
<td>3/5</td>
<td>1/6</td>
<td>1/8</td>
<td>NA</td>
</tr>
</tbody>
</table>

Values are mean±SD where applicable.

Ejection fractions were available for all patients except for one taking propafenone and one control patient. Drug efficacy was defined as suppression of ability to induce sustained ventricular tachycardia.

NA, not applicable.

*The concentrations shown are for the parent drugs. Concentrations of the active metabolite averaged 1.2±0.5 \( \mu \text{mol/l} \) for desethylamiodarone and 0.2±0.1 \( \mu \text{mol/l} \) for 5-hydroxypropafenone.

Methods

Patient Population

The study group consisted of 27 patients receiving class I antiarrhythmic drug therapy for the treatment of cardiac arrhythmias. Eight patients not treated with class I antiarrhythmic drugs served as a control group. All patients were undergoing clinically indicated electrophysiological studies for the assessment of possible tachyarrhythmias (control group) or of the efficacy of antiarrhythmic drug therapy for ventricular tachyarrhythmias. Antiarrhythmic drugs studied were flecainide, propafenone, quinidine, and amiodarone. The clinical characteristics of both patient groups are summarized in Table 1. The results presented for left ventricular ejection fraction were obtained from radionuclide angiography performed as part of the clinical management of each patient.

Electrophysiological Study

The electrophysiological protocol was performed at the beginning of the routine clinical study. All patients gave written consent to the invasive electrophysiological study. A quadrupolar electrode was positioned in the right ventricular apex by way of the right or left femoral vein. Stimulation was performed with 1.5-msec square-wave pulses with twice diastolic threshold current controlled by a programmable stimulator (Bloom Associates, Flying Hills, Pa.). Recordings of electrocardiographic leads I, aVF, and \( V_1 \) and a right ventricular electrogram were obtained at
100 mm/sec paper speed (Mingograf T16, Siemens-Elema, Stockholm, Sweden). Electrocardiographic signals were obtained with electrocardiographic amplifiers (Electronics for Medicine, Pleasantville, N.Y.) with a band width of 0.1 to 100 Hz and a standardized signal amplitude of 1 mV/cm of recording paper. The kinetics of drug-induced blockade were assessed after an abrupt rate change induced by ventricular pacing. Ventricular pacing was initiated during sinus rhythm and was maintained for 1 minute at cycle lengths of 400, 500, and 600 msec. Because the onset of the pacing train was not coupled to the last sinus beat, analysis began with the second ventricular-paced complex, that is, the first ventricular complex at the selected RR interval. Patients were allowed to recover for at least 2 minutes after a series of stimuli at a given rate, which was a time found to be sufficient for the dissipation of all rate-dependent electrocardiographic changes.

Data Analysis

QRS duration was used as an index of ventricular conduction time. Only QRS complexes of consistent morphology were analyzed. Changes in QRS duration resulting from ventricular pacing were measured as a function of heart rate by two observers. Beats 1–10, 15, 20, 25, 30, 40, 50, 60, 70, 80, 90, 100, 110, 120, 130, 140, and 150 were separated (beat by beat), coded, and read by two observers who were unaware of both beat number and treatment received. The observers independently measured QRS duration, using leads they selected as giving the most reliable onset and offset of the QRS complex.

We performed nonlinear regression with a Marquardt procedure (Statgraf software) to fit data to an equation of the form:

$$\text{QRS}_n = \text{QRS}_o + (\text{QRS}_{so} - \text{QRS}_o) \exp \left( -\frac{n}{\tau} \right)$$

Where QRS$_n$, QRS$_o$, and QRS$_{so}$ are the QRS duration of the $n^{th}$ beat, first paced beat, and at steady state, respectively, and $\tau$ is a time constant expressed in terms of a number of beats. The magnitude of rate-dependent conduction slowing was calculated as QRS$_{so}$ minus QRS$_o$ in each study. Analysis was performed separately on measurements obtained by each observer, and the values obtained for $\tau$ and the magnitude of rate-dependent slowing by the two observers were averaged to obtain representative values for each study.

Group data are presented as mean ± SD. The significance of regression was determined by analysis of variance (ANOVA). The statistical significance of differences among time constants and magnitude of rate-dependent slowing for different drugs was assessed by one-way ANOVA with a Scheffé test. The overall significance of each drug as a determinant of the time constant and magnitude of rate-dependent slowing was determined by ANOVA. The statistical significance of differences between values determined at a cycle length of 400 msec and those at 500 msec was determined by paired $t$ tests, by use of only studies during which measurable changes were noted at both cycle lengths. A probability of less than 5% was taken to indicate statistical significance.

Results

In the eight control patients, abrupt changes in heart rate by ventricular pacing did not produce any rate-dependent changes in QRS duration (Figure 1). However, in the presence of class I antiarrhythmic drugs, QRS duration increased progressively as an exponential function of heart rate (Figure 1). Figure 2 shows analog data to illustrate the types of changes in the QRS that occurred after the onset of ventricular pacing at a cycle length of 400 msec, both in the absence and presence of class I antiarrhythmic drugs.

There was excellent agreement between the measurements made by either observer. Figure 3 shows the regression of QRS measurements made by observer 1 on QRS measurements made by observer 2. The correlation coefficient was 0.96 ($p < 0.0001$), and the regression line was close to the line of identity with a slope of 0.94 and an intercept of 9.63 msec. There was also a highly significant correlation ($r = 0.85, p < 0.0001$) between the values of time constants obtained by use of the measurements of either observer. Figure 4 shows the results for an individual patient before and after quinidine therapy as measured by both observers. In this patient, as in the other two patients studied both before and during drug therapy, there were no changes in QRS duration after the onset of ventricular pacing in the control study, but clear use-dependent QRS prolongation occurred during ventricular pacing in the presence of drug therapy. The results obtained by either observer, unaware of heart rate and treatment and measured independently, are quite similar.

The magnitude of rate-dependent conduction slowing depended on pacing cycle length. The time constants of rate-dependent QRS prolongation were estimated separately for data at basic cycle lengths of 400 and 500 msec. Although similar phenomena were observed at a basic cycle length of 600 msec, the magnitude of the changes seen was too small for...
precise calculation. The changes observed were largest at a cycle length of 400 msec, and the curve fits were consequently better than those at 500 msec. Mean time constants for the onset of block are shown in Table 2, with corresponding values for previously reported in vitro studies. In three patients, the changes at a cycle length of 500 msec were too small for the onset time constant to be calculated (one with propafenone and two with flecainide). In two patients taking amiodarone, time constants were only obtained at a cycle length of 500 msec. The time constants for flecainide and propafenone were significantly longer than those for quinidine and amiodarone, and the drug taken was a highly significant determinant of the time constant of rate-dependent QRS prolongation.

Figure 5 shows the relation between time constants measured at a cycle length of 400 msec and those at a cycle length of 500 msec. There was a highly significant correlation between the two sets of results (r=0.89, p<0.0001). Although the magnitude of time-dependent conduction slowing was significantly greater at a cycle length of 400 msec than that at 500 msec (p<0.0001), there was no significant difference between the mean time constants obtained at either cycle length.

Discussion

Class I antiarrhythmic agents are all able to slow ventricular conduction, an action presumably due to the sodium channel blockade that they demonstrate in vitro. Their conduction slowing action has been shown to be qualitatively rate dependent in humans and has potentially important clinical consequences. In the present study, we present data that show for the first time that a variety of class I antiarrhythmic agents produce use-dependent conduction slowing in humans with kinetics similar to those of V_max blockade in vitro.

Determinants of Rate-Dependent Conduction Slowing

There was a close correlation between time constants measured at a cycle length of 400 msec and those measured at 500 msec (Figure 5), and the mean time constants at either rate were not significantly different. While the onset rate constant is expected to decrease at shorter cycle lengths, the magnitude of the change resulting from a decrease in cycle length from 500 to 400 msec in likely to be too small to be detected by the techniques we used. Changes in QRS duration were larger at faster pacing rates, as expected for a rate-dependent phenomenon. This resulted in generally poorer curve fits at slower rates and presumably a lesser precision of the estimated time constants. We, therefore, used the values obtained at a cycle length of 400 msec for comparison with previously reported in vitro data.

As calculated at a cycle length of 400 msec (Table 2), the mean onset time constants ranged from 3.6±2.0 (for amiodarone) to 24.9±11.6 beats (for flecainide). The value we obtained for flecainide is in
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Ranger et al

Control
Pt 17

Amiodarone
Pt 7

Quinidine
Pt 12

Propafenone
Pt 8

Flecainide
Pt 11

Beat number
1  5  20  >100

FIGURE 2. Tracings showing QRS prolongation during ventricular pacing at a cycle length of 400 msec in individual patients taking amiodarone, quinidine, propafenone, and flecainide, as a function of the beat number (in the pacing train) of the complex shown. Corresponding data from a control patient are shown (top). Vertical dotted lines indicate the onset and offset of the QRS complex. We chose points that could be measured accurately and reproducibly rather than try to measure total QRS duration in each case. Small vertical arrows indicate the time of the stimulus artifact. Measured QRS durations are shown at the lower right of each complex, and the patient’s number for each case is given under the drug taken.

FIGURE 3. Regression plot of QRS duration as measured by both observers. There was a highly significant correlation, with the regression line (shown) being close to the line of identity.

the same range as the time constant (34.5 beats) for $V_{\text{max}}$ depression at a cycle length of 300 msec reported in guinea pig papillary muscles by Campbell.\cite{27} Our result for propafenone (17.8±6.9 beats) is similar to the range of values (8–21 beats) for $V_{\text{max}}$ depression in ventricular tissues at cycle lengths of 300–400 msec.\cite{28,29} For quinidine, Valois and Sasyniuk\cite{30} noted an onset time constant of 5.6±0.5 pulses at a cycle length of 600 msec in canine Purkinje fibers, and Grant et al\cite{25} reported a value of 6.2±1.5 pulses at a cycle length of 500 msec. These are quite close to the time constant of 7.0±2.4 beats that we measured at a cycle length of 400 msec. We were unable to find onset time constants for amiodarone to compare with the value (3.6±2.0 beats) that we obtained in humans. However, fitting data of Mason et al\cite{31} (their Figure 1) to a single exponential, we
obtained a time constant for amiodarone of 3 pulses, in the same range as our results. Overall, the values that we measured in humans were in the same range as those reported in vitro, with the same rank order (flecainide > propafenone > quinidine > amiodarone). Comparison is limited by the different experimental animal species tested and by the fact that values are not always available at the same cycle length(s) in vitro as those we studied in humans.

**Potential Limitations**

We used QRS duration as an in vivo index of antiarrhythmic drug-induced conduction slowing. Drug-induced changes in QRS duration are linearly related to directly measured changes in epicardial activation time, provided overall morphology is unchanged (indicating a constant activation pattern). Even though ventricular conduction velocity is proportional to the square root of phase 0 inward current, interval-dependent changes in conduction time approximate a first-order function over the range of values obtained in this study.

We studied patients on therapeutic doses of antiarrhythmic drugs as selected by their treating physicians. Their plasma concentrations (Table 1) were in

**Table 2. Time Constants for the Onset of Drug-Induced Changes in QRS Duration**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Flecainide</th>
<th>Propafenone</th>
<th>Quinidine</th>
<th>Amiodarone</th>
</tr>
</thead>
<tbody>
<tr>
<td>Basic cycle length 500 msec</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>( n )</td>
<td>6</td>
<td>4</td>
<td>6</td>
<td>8</td>
</tr>
<tr>
<td>( r )</td>
<td>0.73±0.08</td>
<td>0.77±0.13</td>
<td>0.69±0.18</td>
<td>0.54±0.18</td>
</tr>
<tr>
<td>Magnitude (msec)</td>
<td>17.4±5.3</td>
<td>21.3±5.9</td>
<td>14.3±6.7</td>
<td>14.4±6.7</td>
</tr>
<tr>
<td>( \tau ) (beats)</td>
<td>26.6±17.3</td>
<td>9.7±2.7</td>
<td>8.4±3.0*</td>
<td>4.4±2.3†</td>
</tr>
<tr>
<td>Basic cycle length 400 msec</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>( n )</td>
<td>8</td>
<td>5</td>
<td>6</td>
<td>6</td>
</tr>
<tr>
<td>( r )</td>
<td>0.89±0.07</td>
<td>0.94±0.04</td>
<td>0.86±0.06</td>
<td>0.85±0.06</td>
</tr>
<tr>
<td>Magnitude (msec)</td>
<td>25.8±5.6</td>
<td>30.0±10.8</td>
<td>26.0±8.9</td>
<td>26.7±13.0</td>
</tr>
<tr>
<td>( \tau ) (beats)</td>
<td>24.9±11.6</td>
<td>17.8±6.9</td>
<td>7.0±2.4†</td>
<td>3.6±2.0‡</td>
</tr>
<tr>
<td>Values reported from in vitro studies</td>
<td>( \tau ) (beats)</td>
<td>34.5±7</td>
<td>8.4±8, 20.8±9</td>
<td>5.6±0, 6.2±5</td>
</tr>
</tbody>
</table>

Values are mean±SD where applicable.

\( n \), number of patients with analyzable kinetic data for drug and cycle length indicated; \( r \), nonlinear correlation coefficient; \( \tau \), time constant.

\( *p<0.05, \#p<0.01, \#\#p<0.001 \) compared with \( \tau \) for flecainide. In addition, \( \tau \) at 400 msec was significantly different between amiodarone and propafenone (\( p<0.01 \)). Overall, drug was a highly significant determinant of \( \tau \), both at cycle length 400 msec (\( p=0.0002 \)) and 500 msec (\( p=0.002 \)).
the therapeutic range, which varies among the drugs selected. This is relevant because the magnitude of drug action, and to some extent the onset time constant, depend on drug concentration. On the other hand, the magnitude of rate-dependent QRS prolongation was not significantly different among the various drugs studied, suggesting that the concentrations achieved were roughly equivalent in biological action. Furthermore, with corrections for protein binding, the concentrations were roughly in the same range as those in the in vitro studies used for comparison.

We cannot exclude the possibility that myocardial ischemia may have contributed to some of the conduction slowing seen. Evidence against a primary role for ischemia is provided by the absence of rate-related slowing in control patients with coronary artery disease, its presence in patients on class I drugs without coronary disease, and the similarity of time constants for conduction slowing by a given drug in vivo and its depression of \( V_{\text{max}} \) in vitro.

**Clinical Relevance**

The similarity between the time constants we observed for rate-dependent QRS prolongation in vivo and the values previously noted for \( V_{\text{max}} \) depression by the same drugs in vitro support the concept that their sodium channel blocking action is responsible for rate-dependent conduction slowing in humans. Such sodium channel blockade is probably responsible for the important QRS prolongation during exercise in patients taking flecainide and propafenone. Rate-dependent conduction slowing by the sinus tachycardia of exercise may be responsible for some cases of proarrhythmia caused by class IC drugs. Evidence for rate-dependent arrhythmogenic mechanisms has been advanced in experimental animal models. Rate-dependent conduction block may play a role in other proarrhythmic actions of class IC agents, such as the facilitation of lethal ventricular tachyarrhythmias during canine acute myocardial ischemia and the potentially detrimental effects of IC drugs in postinfarction patients.

Although amiodarone was not initially classified as a class I antiarrhythmic drug, unlike the other compounds we studied, it clearly has class I properties in vitro and in vivo. Patients taking amiodarone may have QRS prolongation with exercise, which our results suggest are due to use-dependent sodium channel blockade. Amiodarone's use-dependent effects during exercise may be greater in patients with evidence of acute ischemia. This observation may be due to a sensitizing effect of acute ischemia to the drug's sodium channel blocking action. On the other hand, the degree of QRS prolongation by amiodarone at rest in the latter study was greater in the ischemic group, indicating a greater baseline drug effect and itself predicting greater QRS increases with exercise.

Use-dependent conduction slowing by class I drugs may be beneficial in reducing the rate of a ventricular tachycardia. Marchlinski et al showed that ventricular tachycardia slowing by procainamide can be predicted by rate-dependent QRS prolongation. Kidwell et al provided preliminary evidence for use-dependent ventricular tachycardia slowing by flecainide in humans. They estimated a time constant of 15 seconds for the onset of ventricular tachycardia slowing by flecainide, which is in the same range as the time constant we obtained for QRS prolongation (10 seconds at a cycle length of 400 msec).

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**KEY WORDS** • arrhythmias • sodium channel blockers • cardiac conduction • antiarrhythmic drugs • pharmacodynamics
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