Use-Dependent Prolongation of Ventricular Tachycardia Cycle Length by Type I Antiarrhythmic Drugs in Humans

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Background. Type I antiarrhythmic drugs block the cardiac sodium channel in a use-dependent fashion. This use-dependent behavior causes increased drug binding and consequently increased sodium channel blockade at faster stimulation rates. Importantly, the kinetics of drug association and dissociation from the sodium channel differ for each type I antiarrhythmic drug.

Methods and Results. Thirty-five patients receiving type I antiarrhythmic drugs for the treatment of sustained monomorphic ventricular tachycardia (VT) were studied before and after drug therapy. A total of 41 drug studies were performed (lidocaine, n=10; procainamide, n=16; flecainide, n=15). Sustained monomorphic VT of an identical electrocardiographic morphology was induced during the control and follow-up drug studies. During the control study, there was no significant change in the VT cycle length over time. Compared with control, significant prolongation of the onset VT cycle length was observed after treatment with procainamide and flecainide (increase of 52±24 and 80±49 msec, respectively) but not after treatment with lidocaine (increase of 8±37 msec). Additional drug-induced prolongation of the VT cycle length occurred during a 40-second observation period. This secondary “use-dependent” cycle length prolongation contributed significantly to the steady-state VT cycle length during treatment with flecainide (increase of 82±34 msec; p<0.0001). Although a use-dependent increase in VT cycle length was observed with procainamide and lidocaine, the increase was not statistically significant (increase of 12±15 and 8±8 msec, respectively). The estimated time constants for the onset of use-dependent VT cycle length prolongation were distinctly different for the three drugs. Flecainide’s prolongation of the VT cycle length occurred slowly, with an estimated time constant of 12.5±5.0 seconds. In contrast, the time course of VT cycle length prolongation was rapid during treatment with lidocaine and intermediate during treatment with procainamide (time constants of 0.52±0.51 and 4.0±1.3 seconds, respectively).

Conclusions. Use-dependent prolongation of VT cycle length during treatment with type I antiarrhythmic drugs was observed in humans. This effect was clinically significant during treatment with flecainide (i.e., the use-dependent slowing of the heart rate improved the hemodynamic tolerance of the arrhythmia). Finally, the estimated time constants for the use-dependent prolongation of VT cycle length by the three test drugs are similar to their reported in vitro time constants for use-dependent sodium channel blockade. (Circulation 1993;87:118–125)

Key Words • flecainide • lidocaine • procainamide • use dependence • tachycardia, ventricular

Type I antiarrhythmic drugs have been shown to interact with the cardiac sodium channel in a high-affinity, or "use-dependent fashion." Two molecular models have been proposed to explain this behavior.1,4 Hondeghem and Katzung1,2 proposed a "modulated receptor" theory in which cyclical changes in channel receptor affinity are due to a time- and voltage-dependent change in the channel conformation. Starmer, Grant, and Strauss3,4 proposed a "guarded receptor" theory in which channel receptor affinity remains constant but drug-receptor interaction is limited by channel gating. During each cardiac cycle, the sodium channel makes a transition from the resting to the active state. Both models assume minimal drug binding in the resting channel state (low drug affinity versus limited channel access). Membrane depolarization shifts the sodium channels into the active state and increases drug binding. Conversely, repolarization returns the channels to the resting state and promotes drug dissociation from the channel receptors. The rate of this dissociation process is largely responsible for the observed differences in the use dependence of type I antiarrhythmic drugs.5,6 Both models predict that in the presence of type I antiarrhythmic drugs, measures of sodium channel conductivity (Vmax, INa) will progressively decrease as the rate of stimulation increases. Since myocardial conduction velocity is directly related to sodium channel conductivity, it should be possible to quantify in vivo use-dependent effects of type I antiarrhythmic drugs by measuring temporal changes in myo-
cardial conduction intervals. This report details the use-dependent change in ventricular tachycardia (VT) cycle length during treatment with three different type I antiarrhythmic drugs. The acute increase in heart rate associated with the onset of sustained monomorphic VT resulted in a characteristic use-dependent response for each study drug.

Methods

Patient Population

The study group consisted of 35 patients receiving type I antiarrhythmic drugs for the treatment of sustained monomorphic VT. All patients were studied in the drug-free state to assure reproducible induction of sustained VT. This report details the outcome of 41 follow-up drug studies during which sustained monomorphic VT of an identical morphology remained inducible. Antiarrhythmic drugs studied were lidocaine (n = 10), procainamide (n = 16), and flecainide (n = 15). The beat-to-beat cycle lengths of the tachycardia induced on drug therapy were compared with the drug-free state. In all cases except lidocaine, the drug study was performed on a separate day after achieving steady-state oral dosing of the study medication. Lidocaine testing was performed on the day of the control study after acute intravenous administration. Table 1 summarizes the clinical characteristics of the patient groups.

Drug Dosing

Oral antiarrhythmic agents were administered at regular dosing intervals (procainamide, every 6 hours; flecainide, every 12 hours) until steady-state plasma concentrations within the therapeutic range were achieved. Plasma drug levels were obtained at the completion of the stimulation protocol. Lidocaine was administered (after control arrhythmia inductions) as an intravenous bolus of 150 mg followed by a continuous intravenous infusion of 3 mg/min. Lidocaine plasma levels were not routinely obtained.

Electrophysiological Study

Quadripolar pacing catheters were percutaneously introduced and positioned in the right ventricular apex and outflow tract. Surface ECG leads I, aVF, and V1 were continuously recorded. Intracardiac electrograms were amplified (Bloom Associates, Flying Hills, Pa.) with a band width of 50–500 Hz and recorded on a multichannel direct ink jet recorder (Mingograph 800, Siemens-Elema, Stockholm, Sweden) at paper speeds of 100 or 200 mm/sec. Ventricular stimulation was performed with a custom-designed digital stimulator (Bloom Associates) using constant-current rectangular bipolar pulses of 2-msec duration at twice diastolic pacing threshold. Programmed stimulation consisted of the delivery of single, double, and triple extrastimuli after eight-beat drive cycle lengths of 600 and 400 msec. For inclusion into the study group, arrhythmias induced during the control study had to show constancy of cycle length (< 20 msec change in RR interval from onset to termination). In addition, an identical three-lead surface ECG morphology of the induced tachycardias during the control and follow-up drug studies was required. Temporal changes in the beat-to-beat RR interval of the induced arrhythmias were assessed in the control and follow-up drug studies. The RR interval was measured at onset and 1, 2, 3, 4, 5, 7.5, 10, 15, 20, 25, 30, and 40 seconds after the onset of the tachycardia. For purposes of analysis, four primary end points were identified: 1) onset VT cycle length at the control study (Cco), 2) steady-state VT cycle length at the control study (Ccs, t = 30 seconds), 3) onset VT cycle length at the follow-up drug study (Dco), and 4) steady-state VT cycle length at the follow-up drug study (Dcs, t = 40 seconds). Identical induction protocols were performed at the drug-free and follow-up studies. In selected patients, a 5F arterial sheath was placed in the femoral artery to monitor arterial pressure.

Data Analysis

The VT cycle length was considered to reflect the conduction time through a relatively fixed reentrant circuit. It was assumed that the temporal increase in VT cycle length after tachycardia induction was secondary to a use-dependent binding of drug to the sodium channel. After induction of the arrhythmia, beat-to-beat

### Table 1. Clinical Characteristics of Patient Groups

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<tr>
<th></th>
<th>Lidocaine</th>
<th>Procainamide</th>
<th>Flecainide</th>
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<tr>
<td>n</td>
<td>10</td>
<td>16</td>
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<tr>
<td>Age (years)</td>
<td>65±4</td>
<td>62±9</td>
<td>66±9</td>
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<td>Sex (male/female)</td>
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<td>12/4</td>
<td>14/1</td>
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<td>Plasma concentration (mg/l)</td>
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<td>10.9±6.6</td>
<td>0.60±0.16</td>
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<td>Ejection fraction (%)</td>
<td>37±13</td>
<td>39±11</td>
<td>46±5</td>
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<tr>
<td>Control VTCL at onset (msec)</td>
<td>266±43</td>
<td>261±35</td>
<td>250±40</td>
<td>NS</td>
</tr>
<tr>
<td>Control VTCL at steady state (msec)</td>
<td>270±43</td>
<td>253±35</td>
<td>249±41</td>
<td>NS</td>
</tr>
<tr>
<td>Drug VTCL at onset (msec)</td>
<td>275±54</td>
<td>312±40</td>
<td>329±48</td>
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<td>Drug VTCL at steady state (msec)</td>
<td>282±58</td>
<td>324±41</td>
<td>412±54</td>
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<table>
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<td>Dc0–Cco (msec)</td>
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<td>51.4</td>
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<tr>
<td>Dcs0–Dc0 (msec)</td>
<td>10</td>
<td>19</td>
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<td>τ (seconds)</td>
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<td>4.24</td>
<td>12.23</td>
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VTCL, ventricular tachycardia cycle length. ANOVA: p = 0.04, flecainide vs. lidocaine, flecainide vs. procainamide; p = 0.02, flecainide vs. lidocaine, procainamide vs. lidocaine; p = 0.0001, flecainide vs. procainamide, procainamide vs. lidocaine.

*See text for assumption of zero onset block by lidocaine.
changes in the RR interval were measured in all cases. For each induced tachycardia, the control VT cycle length at each time point was subtracted from the corresponding drug cycle length. A nonlinear regression analysis was then performed on the data to find the time constant of the change in tachycardia cycle length (Quasi-Newton least squares fit; SYSTAT version 5.0; Evanston, Ill.) to fit the data to an equation of the form

$$CL_t = CL_{ss} - (CL_{ss} - CL_{oa}) e^{(-t/\tau)}$$

where $CL_t$, $CL_{ss}$, and $CL_{oa}$ represent the VT cycle length at any time $t$, steady state, and onset, respectively. The magnitude and rate constant of the use-dependent prolongation of VT cycle length are represented by $(CL_{ss} - CL_{oa})$ and $\tau$, respectively. The mean temporal data for each study drug were also subjected to regression analysis for clarity of comparative illustration. Group data are expressed as mean ± SD. A paired $t$ test was used to detect differences in control and drug VT cycle lengths at onset and steady state. One-way ANOVA was performed to detect differences in onset and steady-state VT cycle lengths among the study drugs (using a Scheffe test for multiple comparisons).

**Results**

All the patients in this study suffered from a previous myocardial infarction and recurrent scar-related VT. The mean age of the study population was 65 ± 9 years, with a range of 42–78 years. There was no significant difference in age among the three drug groups. A male preponderance was observed in all three drug groups (see Table 1). The mean left ventricular ejection fraction of the study population was 41 ± 11%. However, the ejection fraction of patients studied on flecainide was greater than that of either the IA or IB study groups (46 ± 6 versus 39 ± 11 and 37 ± 13 respectively, $p = 0.04$). This reflects our general practice of restricting the use of this drug to patients with an ejection fraction >39%. Electropharmacological testing was performed to identify an acceptable treatment regimen. A total of 41 drug studies were analyzed. Sixteen patients were studied on a type IA drug (procainamide), 10 were studied on a type IB drug (lidocaine), and 15 were studied on a type IC drug (flecainide). Seven patients were studied on two of the three test drugs.

The control VT cycle length at onset was similar in the three test drug groups and remained similar at steady state (see Table 1). No use-dependent change in the VT cycle length was observed in the drug-free state. After drug administration, the VT cycle length at onset was increased compared with control by both procainamide and flecainide but remained unchanged by lidocaine administration (see Figure 1). This drug-induced increase in onset VT cycle length will be referred to as "onset prolongation." After onset of the tachycardia, additional drug-induced prolongation of the cycle length occurred during a 40-second observation period. This secondary use-dependent prolongation of the VT cycle length contributed significantly to the steady-state VT cycle length during treatment with flecainide (mean onset VT cycle length, 330 ± 48 msec; mean steady-state VT cycle length, 412 ± 54 msec). The additional use-dependent increase in VT cycle length during treatment with lidocaine and procainamide was small.

The use-dependent prolongation of VT cycle length observed with flecainide occurred slowly. Figure 2 shows a plot of consecutive RR intervals after the induction of sustained monomorphic VT in a single patient treated with flecainide. The steady-state VT cycle length ($t=40$ seconds) is 105 msec greater than the onset cycle length. The use-dependent prolongation of VT cycle length occurs slowly, reaching a maximal value after approximately 30 seconds. This slow time course of use-dependent "block" is typical of that observed with

![Figure 1](http://example.com/figure1.png)

**FIGURE 1.** Bar graph shows effect of the different test drugs on mean ventricular tachycardia (VT) cycle lengths. Mean VT cycle length at onset and steady state is shown for both the control and the follow-up drug studies. There was no significant difference in the onset and steady-state VT cycle lengths during the control study for any of the test drugs. Compared with control, a significant increase in the onset VT cycle length was observed during treatment with procainamide and flecainide but not during treatment with lidocaine. Compared with the onset VT cycle length, an additional increase in the tachycardia cycle length was observed at steady state during treatment with flecainide. This secondary "use-dependent" prolongation of the VT cycle length was not significant during treatment with procainamide and lidocaine. Error bars, 1 SD.

![Figure 2](http://example.com/figure2.png)

**FIGURE 2.** Scatterplot demonstrates relation of the use-dependent increase in ventricular tachycardia (VT) cycle length to hemodynamic tolerance of the tachycardia. The beat-to-beat change in VT cycle length and mean arterial pressure are plotted during treatment with flecainide. After onset of tachycardia, the VT cycle length gradually increases from an onset value of 340 msec to a steady-state value of 450 msec (time constant of use-dependent cycle length prolongation, 10.1 seconds). This 110-msec increase in VT cycle length was associated with a parallel increase in the mean arterial pressure (from 75 to 120 mm Hg).
flecainide. In this patient, the arterial pressure was monitored (see analog tracings in Figure 3). The change in VT cycle length was accompanied by a similar temporal increase in mean arterial pressure. The wide variation in mean arterial pressure in this example could be accounted for by variable AV intervals secondary to complete retrograde ventriculoatrial block.

The analog tracings in Figure 4 illustrate characteristic responses of induced VTs during treatment with procainamide and flecainide. This patient received both antiarrhythmic drugs. Consequently, the control tachycardias are identical. Although both drugs increased the onset VT cycle length (procainamide by 110 msec, flecainide by 150 msec), only flecainide was associated with a significant use-dependent prolongation of the cycle length (110-msec increase). The onset and steady-state VT cycle length observed after lidocaine administration was not significantly different from the control VT cycle length (observed increase of 9±11 and 12±8 msec, respectively). In comparison, the mean onset VT cycle length was significantly increased by procainamide (52±24 msec, p=0.0001). The onset prolongation observed with both flecainide and procainamide was significantly greater than that seen with lidocaine (p<0.02). However, during the observation period, procainamide increased the mean VT cycle length by only an additional 19±27 msec compared with the onset value (p<0.01). Patients treated with flecainide demonstrated two distinct components of drug effect (see Figure 1). The onset VT cycle length was prolonged by 81±49 msec compared with control (p=0.0001). However, the most distinctive marker of flecainide's effect was a slowly developing prolongation of the VT cycle length as the tachycardia persisted. This use-dependent prolongation of VT cycle length by flecainide accounted for over 50% (83±58 msec) of the observed increase in tachycardia cycle length. Use-dependent prolongation of VT cycle length by flecainide was significantly greater than that observed with either procainamide or lidocaine (p=0.0001).

The time constants of use-dependent VT cycle length prolongation by the three study drugs were significantly different (flecainide: 12.5±5.0 seconds; range, 6.2–16.3

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**Figure 3.** Representative tracings from a patient during treatment with flecainide. Analog tracings from the patient shown in Figure 2 (flecainide treatment). At onset, the ventricular tachycardia (VT) cycle length is 340 msec and the mean arterial pressure is 75 mm Hg. After 15 seconds of sustained tachycardia, the cycle length has increased to 425 msec and the mean arterial pressure is 100 mm Hg. By 30 seconds, the VT cycle length and arterial pressure increased to 445 msec and 115 mm Hg, respectively. The variation in the steady-state mean arterial pressure could be related to a changing AV interval secondary to complete ventriculoatrial conduction block (see HBE, His bundle electrogram). The tracings are identical for each panel. RVA, right ventricular apical electrogram; surface ECG leads I, aVF, and V1; BP, blood pressure; FS, full scale; femoral arterial pressure recorded at a range of 0–200 mm Hg.

**Figure 4.** Representative drug-induced changes in ventricular tachycardia (VT) cycle length over time: Procainamide vs. flecainide. The patient shown in this example received both procainamide (left panel) and flecainide (right panel) therapy. Consequently, the control tachycardias are identical in both panels. The control VT cycle length was 220 msec at onset and did not change over time. During treatment with procainamide, the VT cycle length increased to 330 msec at onset with an additional 20-msec increase observed at steady state (VT cycle length, 350 msec). During treatment with flecainide, the onset VT cycle length increased to 340 msec. During the next 40 seconds of observation, the tachycardia cycle length increased by an additional 110 msec (steady-state cycle length, 450 msec).
FIGURE 5. Plots show time course of use-dependent ventricular tachycardia (VT) cycle length prolongation by the three test drugs. After onset of tachycardia in the control studies, the cycle length did not change significantly over time. This was true when the data were analyzed for the entire patient group or for each subgroup (plots not shown). After onset of tachycardia during treatment with flecainide, the VT cycle length slowly increased over time. This temporal change in the mean VT cycle length was fit by a nonlinear regression (see “Methods”) with a time constant of 12.2 seconds. In contrast, the time course of the use-dependent increase in the tachycardia cycle length associated with procainamide was more rapid. The estimated time constant for procainamide-induced prolongation of the mean VT cycle length was 4.2 seconds. Finally, treatment with lidocaine was associated with no significant use-dependent change in the VT cycle length. However, given lidocaine’s rapid in vitro kinetics, it can be assumed that the change in onset VT cycle length was use dependent in origin. Consequently, a theoretical zero point was plotted along with the observed lidocaine data (see text). With this assumption in mind, the estimated time constant for the increase in tachycardia cycle length during treatment with lidocaine was found to be 0.57 seconds. Error bars, 1 SD.

seconds; procainamide: 4.0±1.3 seconds; range, 1.8–6.0 seconds; lidocaine: 0.52±0.51 seconds; range, 0.2–1.6 seconds). The second panel in Figure 5 shows a plot of the mean change in VT cycle length during treatment with flecainide (n=15). The mean data were well fit by an exponential with a time constant of 12.2 seconds (r²=0.99). Although the magnitude of use-dependent prolongation of VT cycle length by procainamide was clinically insignificant, the time course of the effect could be readily appreciated. Panel 3 in Figure 5 shows a plot of the mean change in VT cycle length during treatment with procainamide (n=16). Compared with the onset value, the VT cycle length only increased an additional 19 msec. However, the steady-state cycle length was reached much more quickly during treatment with procainamide. The mean procainamide data were fit by an exponential with a time constant of 4.2 seconds (r²=0.96). No use-dependent block was observed during treatment with lidocaine (n=10); nevertheless, a small increase in the mean VT cycle length was observed compared with the drug-free study. In vitro experiments suggest that during repolarization, lidocaine dissociates rapidly from the sodium channel (time constant, <0.2 seconds). At a heart rate of 100 beats per minute (i.e., during the induction drive), approximately 95% of the sodium channels blocked by lidocaine should become unblocked before the next stimulated impulse. With this in mind, a theoretical zero time point (equal to the mean onset VT cycle length during the control study) was plotted along with the mean lidocaine data (panel 4, Figure 5). These data were fit by an exponential with a time constant of 0.57 seconds (r²=0.86). It should be emphasized that our experimental design does not permit an accurate estimate of lidocaine’s time constant of use-dependent VT cycle length prolongation. However, if the above assumption is valid, it is unlikely that lidocaine’s time constant of use-dependent VT cycle length prolongation is greater than our estimate.

Discussion

The temporal changes in the VT cycle length observed in this report were consistent with a use-dependent effect of the study drugs on myocardial conduction within the reentrant circuit. During the control study, the steady-state VT cycle length was not significantly
different from the onset cycle length. However, during the follow-up drug studies, a gradual prolongation of the VT cycle length was observed. The time course of VT cycle length prolongation was characteristic for each study drug. Flecainide produced a slow but progressive increase in VT cycle length (time constant, 12.5 seconds). In contrast, the increase in VT cycle length appeared to be instantaneous with lidocaine (time constant <0.6 seconds). Prolongation of the VT cycle length by procainamide occurred with an intermediate time constant (4.0 seconds).

Relation of Changes in Sodium Conductance to Changes in Conduction Velocity

Type I antiarrhythmic drugs have been shown to cause a use-dependent decrease of INa in myocardial cells. Although similar use-dependent reductions of measurable Vmax and conduction velocity by type I drugs have been reported, the relation of Vmax and conduction velocity to INa was debated. Sheets and coworkers studied the use-dependent effects of quinidine on both INa and Vmax in isolated canine cardiac Purkinje cells. Their experiments demonstrated a nonlinear relation between INa and Vmax (at temperatures between 0° and 27°C). Although Vmax failed to accurately reflect voltage-dependent changes in INa, the time course of the use-dependent decrease of INa and Vmax was similar. Buchanan and coworkers demonstrated that the experimental relation between Vmax and conduction velocity was similar to that predicted by classic cable theory—that is, the changes in Vmax were proportional to the square of the changes in conduction velocity. This relation was confirmed over a wide range of stimulation frequencies (0.1–8 Hz) and in the presence of lidocaine, quinidine, and procainamide. Additional type I antiarrhythmic drugs have been shown to affect Vmax and myocardial conduction in a similar manner. Nattel confirmed this relation for lidocaine in canine cardiac Purkinje fibers and suggested that the use dependence of antiarrhythmic drug action should be amenable to in vivo quantification by the measurement of myocardial conduction delay.

The change in VT cycle length produced by the type I drugs in this report is consistent with a use-dependent decrease in myocardial conduction velocity. This conclusion assumes that the reentrant pathway remains constant. We attempted to control this variable by including only patients with stable monomorphic tachycardias that were identical in morphology during the control and follow-up drug study. Of course, minor changes in the local activation pathway may have occurred without producing detectable changes in the surface ECG pattern. The extent to which this may be responsible for the observed use-dependent changes in tachycardia cycle length remains uncertain. However, it should be noted that no significant change in the cycle length of the tachycardia occurred during the drug-free state. This along with the characteristic use-dependent response of the test drugs suggests that the observed cycle length prolongation was secondary to drug-induced slowing of myocardial conduction over a relatively fixed reentrant pathway.

Comparison With In Vitro Findings

The time course of in vitro use-dependent depression of Vmax by type I antiarrhythmic drugs has been well characterized. In our study, the estimated onset time constants of the tested antiarrhythmic drugs ranged from 0.52 seconds for lidocaine to 12.5 seconds for flecainide. Use-dependent conduction delay was most apparent during treatment with flecainide. Fifty percent of the increase in VT cycle length observed with flecainide was related to use-dependent cycle length prolongation (81±49 msec of onset prolongation versus 83±58 msec of use-dependent prolongation). The estimated time constant of flecainide’s use-dependent cycle length prolongation is consistent with the reported time constants of use-dependent Vmax depression by flecainide (8.4–12.3 seconds). Our result for procainamide is also similar to that reported for in vitro Vmax depression (4.4–5.0 seconds). Many reports have described the in vitro effects of lidocaine on Vmax. The time constant of lidocaine’s in vitro use-dependent reduction of Vmax is rapid (<0.2 seconds). In our report, no significant use-dependent prolongation of VT cycle length was observed during treatment with lidocaine. However, the onset VT cycle length was slightly increased compared with the control value. Since lidocaine’s in vitro dissociation time constant is considerably less than the induction pace cycle length (200 versus 600 msec), we reasoned that no significant onset cycle length prolongation should occur with lidocaine. If this assumption is valid, our estimation of lidocaine’s onset time constant (0.52 seconds) is likely to represent the upper limit of the true value. Our protocol was limited by the intrinsic cycle length of the induced tachycardias—faster rates of in vivo stimulation would be required to adequately test drugs with rapid in vitro kinetics. As suggested by Nattel, an assessment of the change in myocardial conduction with closely coupled ventricular extrasystoles may provide a closer approximation of lidocaine’s onset time constant.

Comparison With Other Clinical Studies

Few reports have detailed the kinetic behavior of type I antiarrhythmic drugs on myocardial conduction in humans. Gang and coworkers demonstrated a rate-dependent increase in the HV interval after procainamide administration in humans. Similarly, Morady and coworkers demonstrated a rate-dependent prolongation of the paced QRS duration in the presence of lidocaine, procainamide, and amiodarone. Marchlinski and coworkers were able to correlate the rate-related increase in the paced QRS duration with the increase in VT cycle length during treatment with procainamide. However, none of these reports addressed the kinetics of the drug-induced conduction delay. Ranger and coworkers reported a progressive, rate-related increase in the measured QRS duration during exercise in patients treated with flecainide. Although a correlation between the heart rate and the observed QRS prolongation was observed, the onset kinetics of flecainide’s use-dependent QRS prolongation could not be appreciated by Ranger’s study. A similar exercise-related increase in QRS duration has been reported during treatment with amiodarone. Ranger and his colleagues extended their findings by testing the in vivo onset kinetics of several antiarrhythmic drugs with a pacing protocol in humans. They studied the effect of rapid ventricular pacing (cycle lengths of 300 and 400 msec) on the QRS duration during treatment with
flecainide, propafenone, quinidine, and amiodarone. The mean time constants for the onset of drug-induced QRS prolongation in their study were: flecainide, 10 seconds; propafenone, 7.1 seconds; quinidine, 2.8 seconds; and amiodarone, 1.4 seconds. Importantly, they did not observe a use-dependent increase in the QRS duration in a group of age- and disease-matched control patients. These values are similar to the reported time constants for the in vitro depression of \( V_{\text{max}} \) by these drugs, and their reported time constant for flecainide’s use-dependent QRS prolongation is similar to our estimate of flecainide’s time constant for use-dependent VT cycle length prolongation.

**Onset Versus Use-Dependent VT Cycle Length Prolongation**

The term “tonic block” has been used to describe the residual in vitro drug-induced reduction of \( V_{\text{max}} \) after a long resting period in a repolarized state. This rest period is sufficiently long (in relation to the drug’s dissociation constant) to allow complete dissipation of use-dependent sodium channel blockade. A resting period of this duration cannot be achieved in a clinical protocol—especially in the case of a drug with slow use-dependent kinetics. Consequently, the drug-induced change in the onset VT cycle length observed in our study should be considered to result from both tonic block and the use-dependent block incurred at the basic pace cycle length. A significant increase in the onset VT cycle length was observed with both flecainide and procainamide but not with lidocaine (see Table 1 and Figure 4). This difference in the three test drugs is consistent with their derived time constants of use-dependent conduction delay. The time constants for both flecainide and procainamide significantly exceed the basic drive cycle length. Consequently, significant drug-induced prolongation of the onset VT cycle length is expected. The time constant for lidocaine is sufficiently rapid to allow nearly complete dissipation of block after each stimulated impulse. Consequently, an insignificant change in the onset VT cycle length should be expected with lidocaine.

**Limitations**

Interpretation of the cycle length changes observed in this study as a use-dependent sodium channel blocking effect requires that activation proceeds over a fixed reentrant pathway. Alternatively, it is arguable that the change in tachycardia cycle length was secondary to a changing conduction pathway. The findings favoring a use-dependent sodium channel blocking effect are 1) an insignificant change in the VT cycle length during the control study, 2) a uniform QRS morphology associated with the change in VT cycle length, and 3) distinct use-dependent time constants for each of the three test drugs. The last observation provides the strongest support for our conclusions, and the rank order of the time constants are consistent with known in vitro kinetics (flecainide > procainamide > lidocaine).

Voltage-dependent sodium channel inactivation (i.e., phase 3 block) could account for myocardial conduction delay during rapid ventricular pacing or tachycardia. This mechanism is unlikely to account for our observations. First, this effect would be more likely to occur during the control tachycardia inductions (because of their faster rates). Second, if present, phase 3 conduc-

tion delay should demonstrate “reverse” use dependence (i.e., progressive improvement in conduction) because of the expected rate-related shortening of the action potential duration.

Our protocol was limited to observation of the rate-related changes in myocardial conduction associated with an abrupt onset of tachycardia. Although this protocol is capable of illustrating the use-dependent effect of a drug with slow onset kinetics (flecainide), it is inadequate to fully characterize the in vivo effects of a drug with rapid onset kinetics (lidocaine). At the cycle lengths tested, lidocaine would be expected to demonstrate minimal use-dependent cycle length prolongation.

**Clinical Implications**

Recent reports have emphasized the potential deleterious or proarrhythmic risks of type I antiarrhythmic drug therapy. In particular, the rate-dependent conduction slowing associated with the type IC drugs (flecainide, encainide) has been implicated as a potential mechanism for drug proarrhythmia. In a theoretical model, Starmer and coworkers have demonstrated that drugs with slow use-dependent kinetics are capable of increasing the duration of a “vulnerable window” during which premature stimuli are capable of causing unidirectional block and reentrant activation. This proarrhythmic drug response was enhanced at faster stimulation rates. Further evidence for use-dependent type I proarrhythmia has been demonstrated in animal models and Myerburg et al have suggested that type IC proarrhythmia may be reversed by treatment with propranolol. Our report clearly demonstrates that use dependence can contribute significantly to the observed sodium channel blocking effect of type I drugs—particularly type IC drugs such as flecainide. This effect may not always be detrimental. The use-dependent increase in VT cycle length observed during flecainide treatment in this study was generally associated with improved hemodynamic tolerance of the tachycardia. However, the probability of benefit from this use-dependent effect must be balanced against the possibility of an increased spontaneous event rate. The relation of these proarrhythmic and antiarrhythmic drug effects to sodium channel blocking kinetics remains uncertain.

**References**

6. Campbell TJ: Kinetics of onset of rate-dependent effects of class I antiarrhythmic drugs are important in determining their effects on refractoriness in guinea pig ventricle and provide a theoretical basis for their subclassification. *Cardiovasc Res* 1983;17:344–352.
7. Varro A, Elharrar V, Surawicz B: Frequency-dependent effects of several class I antiarrhythmic drugs on \( V_{\text{max}} \) of action potential.


Use-dependent prolongation of ventricular tachycardia cycle length by type I antiarrhythmic drugs in humans.
G A Kidwell, A J Greenspon, R M Greenberg and K J Volosin

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