Rate-Dependent Effects of Intravenous Lidocaine, Procainamide and Amiodarone on Intraventricular Conduction

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In this study, the duration of the QRS complex during ventricular pacing was used as an index of intraventricular conduction to quantitate the rate-dependent effects of intravenous lidocaine, procainamide and amiodarone. Right ventricular apical pacing (15 to 20 beats) was performed at cycle lengths of 600, 500, 400, 350, 300, 275 and 250 ms, before and 5 minutes after the intravenous administration of lidocaine in 11 patients (serum level 3.2 ± 0.8 µg/ml [mean ± SD]), procainamide in 14 patients (serum level 8.2 ± 1.9 µg/ml) and amiodarone in 12 patients (serum level 3.9 ± 1.2 µg/ml). Electrocardiographic recordings were made at a paper speed of 150 mm/s. QRS duration was measured in a blinded fashion, with reproducibility within 5%.

In the control state, QRS duration was the same at all paced cycle lengths. After lidocaine, procainamide and amiodarone administration, the shortest paced cycle length with complete ventricular capture was 250 ± 0, 275 ± 38 and 264 ± 20 ms, respectively. At a paced cycle length of 600 ms, the increase in QRS duration compared with the control state was 1 ± 2% with lidocaine (p > 0.05), 21 ± 7% with procainamide (p < 0.001) and 6 ± 6% with amiodarone (p < 0.05). At the shortest paced cycle length with complete capture, the increase in QRS duration compared with the control state was 20 ± 6% with lidocaine (p < 0.001), 42 ± 11% with procainamide (p < 0.001) and 26 ± 4% with amiodarone (p < 0.001).

The acute effects of lidocaine, procainamide and amiodarone on intraventricular conduction are rate-dependent, with the effects of intravenous amiodarone being more similar to those of lidocaine than those of procainamide. Prolongation of conduction occurs at a slower rate with procainamide than with lidocaine or amiodarone. These data suggest that each of these three drugs blocks sodium channels, and that recovery from block is slower with procainamide than with lidocaine or amiodarone.

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Methods

Patients studied. Thirty-seven patients (24 men and 13 women) who underwent electrophysiologic testing because of ventricular tachycardia or unexplained syncope were the subjects of this study. Their mean age (± SD) was 58 ± 15 years. Twenty-three patients had coronary artery disease, eight had a dilated cardiomyopathy, one had mitral valve prolapse and five had no identifiable structural heart disease.

Pacing protocol. Electrophysiologic testing was performed with the patients in the fasting, unsedated state after informed consent had been obtained, at least four half-lives after discontinuation of all antiarrhythmic drugs. One to three 6F quadripolar electrode catheters were positioned at various locations in the right atrium or ventricle, as clinically indicated. The pacing protocol (outlined later) was performed in the course of electropharmacologic testing in patients who had inducible ventricular tachycardia, or on completion of a normal electrophysiologic study in patients who had unexplained syncope.

A quadripolar electrode catheter was positioned in the apex of the right ventricle. Pacing was performed at a current strength of twice diastolic threshold (pulse width 2 ms) with a programmable stimulator (Bloom Associates, Ltd.). In all patients, the pacing threshold was less than 1 mA. Right ventricular pacing was performed for at least 15 to 20 beats at cycle lengths of 600, 500, 400, 350, 300, 275 and 250 ms. The last five QRS complexes of each pacing train were recorded on an Electronics for Medicine VRI2 recorder, at a paper speed of 150 mm/s. Electrocardiographic leads V_2, I and III were recorded. This pacing protocol was performed immediately before and 5 minutes after the administration of lidocaine in 11 patients, procainamide in 14 patients and amiodarone in 12 patients. The electrode catheter positioned in the right ventricular apex was not moved in the interim.

The following intravenous dosing protocols were used: 1) lidocaine: 100 mg over 2 minutes, followed by three 50 mg boluses at 5 minute intervals; a 2 mg/min continuous infusion was started immediately after the initial 100 mg bolus; 2) procainamide: 1 g at a rate of 50 mg/min; and 3) amiodarone: 10 mg/kg at a rate of 50 mg/min. A blood sample for determination of the appropriate serum drug level was drawn after completion of the pacing protocol (10 to 15 minutes). The mean serum levels of lidocaine, procainamide and amiodarone were 3.2 ± 0.8 μg/ml (range 1.7 to 4.3), 8.2 ± 1.9 μg/ml (range 6.1 to 10.2) and 3.9 ± 1.2 μg/ml (range 2.1 to 4.8), respectively.

Data analysis. The duration of the QRS complex was measured from electrocardiographic lead III which, in all cases, provided the best definition of the onset and termination of the QRS complex. Patients were not included in this study if the onset or termination of the QRS complex was not well defined in any of the three monitored electrocardiographic leads. The duration of the last QRS complex of each paced train was measured in a blinded fashion by one of us (F.M.). Reproducibility, as assessed by independent measurement of the QRS complexes by another one of us (L.O.) was within 5%.

All values are expressed as mean ± standard deviation. Statistical analysis was performed with paired or unpaired t test, as appropriate.

Results

In the control state, there was no significant difference in the QRS duration during ventricular pacing at the various cycle lengths. The shortest cycle length resulting in complete ventricular capture was 260 ± 15 ms. The rate-dependent effects of lidocaine, procainamide and amio-
Figure 2. Rate-dependent effects of procainamide on QRS duration. Format as in Figure 1.

Effects of lidocaine (Fig. 1 and 4). After the administration of lidocaine, at a paced cycle length of 600 ms, there was no change in QRS duration compared with the control state (164 ± 24 versus 162 ± 24 ms, p > 0.05). In all 11 patients who received lidocaine, there was complete ventricular capture at a paced cycle length of 250 ms. After lidocaine, at a paced cycle length of 250 ms, there was a 21% increase in QRS duration compared with the control state (194 ± 30 versus 160 ± 24 ms, p < 0.001).

Effects of procainamide (Fig. 2 and 5). After procainamide administration, at a paced cycle length of 600 ms, there was a 21% increase in QRS duration compared with the control state (193 ± 30 versus 160 ± 15 ms, p < 0.001). In nine patients, the shortest cycle length resulting in complete ventricular capture was 250 ms, and in five patients, it was 300 or 350 ms (mean 273 ± 12). At the

Figure 3. Rate-dependent effects of amiodarone on QRS duration. Format as in Figure 1.
shortest paced cycle length resulting in complete ventricular capture, there was a 41% increase in QRS duration compared with the control state (232 ± 37 versus 164 ± 25 ms, p < 0.001).

**Effects of amiodarone (Fig. 3 and 6).** After amiodarone administration, at a paced cycle length of 600 ms, there was a 6% increase in QRS duration compared with the control state (160 ± 26 versus 152 ± 29 ms, p < 0.05). In eight patients, the shortest paced cycle length resulting in complete ventricular capture was 250 ms, and in three patients, it was 275 or 300 ms (mean 262 ± 21). At the shortest paced cycle length resulting in complete ventricular capture, there was a 26% increase in QRS duration compared with the control state (190 ± 38 versus 150 ± 28 ms, p < 0.001).

**Comparison of drug effects (Table 1).** At a paced cycle length of 600 ms, the increase in QRS duration compared with the control state after procainamide was significantly greater than after lidocaine or amiodarone (p < 0.001 for both), and the increase after amiodarone was significantly greater than that after lidocaine (p < 0.001). At the shortest paced cycle length resulting in complete ventricular capture, the increase in QRS duration compared with the control state was significantly greater after procainamide than after lidocaine or amiodarone (p < 0.001 for both), and the increase after amiodarone was significantly greater than that after lidocaine (p < 0.05).

**Discussion**

The results of this study indicate that intravenous lidocaine, procainamide and amiodarone all acutely prolong intraventricular conduction in a rate-dependent manner. Because sodium channel blockade is reflected by intraventricular...
Figure 6. A typical example of the rate-dependent effect of intravenous amiodarone on QRS duration. In the control state, QRS duration was 173 ms at a paced cycle length of 600 and 250 ms. After amiodarone administration (serum level 3.8 μg/ml), QRS duration increased by 12% to 193 ms at a paced cycle length of 600 ms, and by 31% to 227 ms at a paced cycle length of 275 ms. At a paced cycle length of 250 ms, there was 2:1 ventricular capture. *Values are expressed as mean ± SD. CL = cycle length.

Table 1. Percent Change in QRS Duration After Lidocaine, Procainamide and Amiodarone Administration at a Ventricular Paced Cycle Length of 600 ms and at the Shortest Paced Cycle Length Resulting in Complete Ventricular Capture

<table>
<thead>
<tr>
<th>Percent change in QRS</th>
<th>Lidocaine (11 patients)</th>
<th>Procainamide (14 patients)</th>
<th>Amiodarone (12 patients)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paced CL 600 ms</td>
<td>(A) 1 ± 2 (B) 21 ± 7 (C) 6 ± 6</td>
<td></td>
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</tr>
<tr>
<td>Shortest paced CL</td>
<td>(D) 20 ± 6 (E) 42 ± 11 (F) 26 ± 4</td>
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<tr>
<td>with complete capture</td>
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</tr>
<tr>
<td>Shortest paced CL</td>
<td>(G) 250 ± 0 (H) 275 ± 38 (I) 264 ± 20</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(ms)</td>
<td></td>
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<tr>
<td>p Values</td>
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<tr>
<td>p &lt; 0.001 = D vs. A, E vs. B, F vs. C, B vs. A, B vs. C, C vs. A, E vs. D, E vs. F; p &lt; 0.01 = H vs. G; p &lt; 0.05 = F vs. D; p &gt; 0.05 = H vs. I, I vs. G.</td>
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Results of prior studies. In a preliminary report (9), the rate-dependent effects on QRS duration of intravenous procainamide and lidocaine and oral amiodarone and mexiletine were tested in groups of three to five patients each. With each drug, the QRS duration at a short ventricular pacing cycle length (290 ± 34 ms) was 10 to 12% greater than at a ventricular pacing cycle length of 500 ms. When the results of our study were analyzed in a similar fashion, intravenous lidocaine, procainamide and amiodarone were found to increase the QRS duration at a ventricular pacing cycle length of 300 ms to a value 10 to 11% greater than at a cycle length of 500 ms. Our results therefore confirm these preliminary observations; however, they also highlight the contrasting effects of the three drugs since the study compared pre- and post-drug QRS duration at various pacing cycle lengths, rather than only QRS duration at long and short pacing cycle lengths after drug administration.

Effects of lidocaine. Lidocaine administration had little or no measurable effect on intraventricular conduction at a cycle length of 600 ms; depression of intraventricular conduction by lidocaine was manifest only at the more rapid pacing rates. In contrast, two prior studies (7,8) of the effects of lidocaine on intraventricular conduction in human subjects concluded that this drug did not have rate-dependent effects on conduction. However, the dose of lidocaine administered in these prior studies was only 50 to 150 mg and may not have yielded an adequate serum drug level. In addition, in these studies, intraventricular conduction was assessed by measurement of QRS duration during atrial pacing. The assessment of rate-dependent effects was therefore limited by the occurrence of atrioventricular nodal Wenckebach block. The use of ventricular pacing in our study avoided this limitation and allowed the attainment of more rapid rates than is possible with atrial pacing.

Effects of procainamide. In contrast to the effects of lidocaine, procainamide slowed conduction to a significant degree (21%), even at a paced cycle of 600 ms. This suggests that there is more rapid recovery of blocked sodium channels with lidocaine than with procainamide, such that at an interstimulus interval of 600 ms, recovery of sodium channels blocked by lidocaine is complete or nearly complete and no measurable prolongation of intraventricular conduction is observed. These findings are compatible with the results of in vitro studies (2) indicating that the recovery half-time of sodium channels blocked by lidocaine is 140 ms, whereas the corresponding recovery half-time in the case of procainamide is 1.8 seconds. These findings also explain why procainamide increases QRS duration during sinus rhythm whereas lidocaine does not (10), even though both drugs block sodium channels.

Effects of intravenous amiodarone. The acute rate-dependent effects of intravenous amiodarone on intraventricular conduction, these findings are consistent with rate-dependent sodium channel blockade found previously (1-4) to occur in vitro in response to lidocaine, procainamide and amiodarone.
ular conduction were intermediate to the effects of lidocaine and procainamide, with mild prolongation (6%) at a paced cycle length of 600 ms, and a maximal prolongation of 26% at the more rapid stimulation rates. The acute effects of intravenous amiodarone more closely resembled the effects of lidocaine than those of procainamide. In contrast, in vitro studies (4) have indicated that the time constant for recovery of sodium channels from amiodarone blockade is long (1.8 seconds), suggesting that significant prolongation of intraventricular conduction should occur at a paced cycle length of 600 ms. There are three possible explanations for this apparent discrepancy. First, although the serum amiodarone level in every patient tested with this drug was within or above the range of serum levels reported to be "therapeutic" for intravenous amiodarone (2 to 3 µg/ml) (11) because the pacing protocol was performed only 5 minutes after completion of the amiodarone infusion, there may not have been adequate time for amiodarone to move from the intravascular into the tissue compartment. Second, because sodium channel blockade caused by amiodarone administration is both rate-dependent and voltage-dependent (4), the discrepancy may be attributed to voltage differences between the intact heart and isolated muscle preparations. Finally, there may be a difference between the rate-dependent effects of amiodarone in animals and human subjects.

Intravenous amiodarone in treatment of ventricular tachycardia. There has been disagreement regarding the acute efficacy of intravenous amiodarone for the treatment of ventricular tachycardia. Some studies (11-16) reported that intravenously administered amiodarone is efficacious in the acute suppression of both spontaneous and induced ventricular tachycardia and ventricular premature depolarizations. However, other studies (17,18) concluded that intravenous amiodarone has no acute antiarrhythmic effects on ventricular arrhythmias. Although some investigators (4) concluded that amiodarone has primary effects on the myocardial action potential which could account for its antiarhythmic effects, others (19,20) found that the antiarrhythmic effects of amiodarone may be mediated by a disturbance in thyroid metabolism. The results of our study suggest that amiodarone does have a direct depressant effect on conduction through ventricular myocardium. This effect occurred acutely and cannot be explained by an alteration in thyroid metabolism. Intravenous amiodarone has little or no acute effect on ventricular refractoriness (15,16,18,21). Therefore, rate-dependent effects of amiodarone on intraventricular conduction may provide a potential mechanism of action by which intravenous amiodarone suppresses ventricular arrhythmias.

No comments were made in this study on the relation between QRS duration during sinus rhythm, presence of bundle branch block or duration of HV interval and rate-dependent effects on conduction because very few patients studied had bundle branch block or a prolonged HV interval.

Conclusions. Lidocaine, procainamide and amiodarone all acutely prolong intraventricular conduction in a rate-dependent fashion. The findings of this study provide in vivo corroboration of in vitro data indicating that each of these drugs blocks sodium channels. The rate-dependent response to these drugs suggests that recovery of blocked sodium channels occurs most rapidly with lidocaine, and least rapidly with procainamide.

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References
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