Effect of Lidocaine and Quinidine on Steady-State Characteristics and Recovery Kinetics of (dV/dt)\textsubscript{max} in Guinea Pig Ventricular Myocardium

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ABSTRACT

We studied the effects of quinidine and lidocaine on the steady-state relationship between membrane potential and the maximum rate of rise of the action potential, (dV/dt)\textsubscript{max}, and on the recovery kinetics of (dV/dt)\textsubscript{max} in guinea pig papillary muscles. The steady-state relationships were determined in fibers stimulated at 0.2/sec and depolarized with KCl. Recovery kinetics were determined at various resting membrane potentials by assessing (dV/dt)\textsubscript{max} in progressively earlier premature action potentials. Lidocaine caused a dose-dependent decrease in (dV/dt)\textsubscript{max}, shifted the curve defining the steady-state relationship along the voltage axis in the direction of more negative potentials, and slowed the recovery kinetics of (dV/dt)\textsubscript{max}. Quinidine caused a dose-dependent decrease in (dV/dt)\textsubscript{max} but did not alter the shape of the curves defining either the steady-state relationship or the recovery kinetics of (dV/dt)\textsubscript{max}. Both drugs depressed membrane responsiveness as determined in premature action potentials originating from incompletely repolarized fibers. Our study indicates that the mechanisms whereby quinidine and lidocaine influence (dV/dt)\textsubscript{max} are different. It is possible that this difference may underlie some of the differences in the clinical effects of these two drugs.
Effects of Drugs on \((dV/dt)_{\text{max}}\)

state and recovery characteristics of \((dV/dt)_{\text{max}}\) and thus to define more precisely the similarities and differences in the mode of action of the two drugs. These drugs were chosen because they exert different effects on QRS duration and intraventricular conduction (3).

Methods

The experiments were conducted on guinea pig right ventricular papillary muscles mounted in a three-compartment single sucrose-gap chamber (10). The proximal and distal compartments of the muscle chamber were perfused at a constant rate of 1.7 ml/min with normal Tyrode’s solution having the following millimolar composition: NaCl 137, KCl 5.4, CaCl₂ 1.8, MgCl₂ 1.0, NaHCO₃ 11.9, NaH₂PO₄ 0.42, and glucose 5. The Tyrode’s solution was equilibrated with 95% O₂-5% CO₂ and the pH ranged between 7.2 and 7.4. The middle compartment of the chamber was perfused with isotonic sucrose solution equilibrated with 100% O₂. The temperature was maintained at 37 ± 0.2°C.

Transmembrane potentials were recorded from the proximal muscle end with two standard 3M KCl-filled glass microelectrodes, one intracellular and the other extracellular, placed closely together. These electrodes were coupled by Ag-AgCl wire to a differential amplifier having a high input impedance and variable capacity neutralization.

The upstroke of the action potential was electronically differentiated to yield a spike that precisely measured the maximum rate of depolarization, \((dV/dt)_{\text{max}}\). This measurement was linear from 10 to 1000 v/sec. The transmembrane action potentials and the differentiated upstrokes were displayed on a dual-beam cathode ray oscilloscope (Tektronix model 565) and photographed on Polaroid or 35-mm film.

To determine the steady-state effects of the studied drugs, the fibers were stimulated at a rate of 0.2/sec by rectangular pulses 4 msec in duration and 1.2-1.8 times diastolic threshold in strength (less than 20 μAmp). This nonphysiological rate was chosen to ensure the complete recovery of the action potential parameters between each excitation. The membrane potential-\((dV/dt)_{\text{max}}\) relationship was determined by depolarizing the fiber from its original resting potential of ~80 to ~90 mV to approximately ~60 mV by adding small quantities of 500 mM KCl to the solution perfusing the test compartment. This procedure raised the potassium concentration in the test compartment to approximately 20 mM. The justification for this method has been previously described (6). The method for determining the recovery kinetics of \((dV/dt)_{\text{max}}\) has also been previously described (6). In brief, a single test (or premature) stimulus 4 msec in duration was introduced from a second stimulator in series with and triggered by the first stimulus after every eighth basic or conditioning response. The interval between the conditioning and premature stimuli was progressively decreased, and \((dV/dt)_{\text{max}}\) in the premature response was expressed as a function of the interval between the end (within 1.0 mV) of the conditioning action potential and the onset of the premature action potential (see Fig. 6). This interval is referred to as the test interval. Because threshold current intensity varies as a function of resting potential, stimulus interval, and drugs, the premature stimulus strength was adjusted to maintain a constant interval between the stimulus artifact and the upstroke of the action potential and did not exceed 2.5 times diastolic threshold. In both a prior study (6) and in this study, varying the stimulus duration between 1 and 5 msec was found to have no effect on \((dV/dt)_{\text{max}}\) or on the recovery kinetics of \((dV/dt)_{\text{max}}\).

In each experiment, determinations were made before and 30 minutes after the addition of 4–16 μg/ml (0.77–3.08 × 10⁻⁵ M) of quinidine gluconate or 4–16 μg/ml (1.72–6.87 × 10⁻⁵ M) of lidocaine HCl. In all experiments, the microelectrode was maintained in the same cell before and after the addition of the drug to the perfusate. In some experiments, the effects of lidocaine and quinidine were tested during the continuous impalement of the same fiber. This procedure is justified because the effects of lidocaine are readily reversible (11, 12). In these experiments, the effects of lidocaine were assessed first. The control observations were then repeated 30–60 minutes after perfusion with lidocaine-free solution had been started. If the control observations were identical to the prelidocaine results, the effects of quinidine were assessed.

Results

Effects of Lidocaine on the Steady-State Characteristics of \((dV/dt)_{\text{max}}\)

The effects of lidocaine were assessed in seven experiments. Lidocaine caused a dose-dependent decrease in steady-state \((dV/dt)_{\text{max}}\) that ranged from 6% to 20% when the resting potential was more negative than ~85 mV. The decrease in \((dV/dt)_{\text{max}}\) became more pronounced when the resting potential was made less negative than ~80 mV. These effects of lidocaine are illustrated by the results shown in Figures 1 and 2. In Figure 1, the effects of 6 μg/ml of lidocaine on \((dV/dt)_{\text{max}}\) at resting potentials of ~87 mv and ~66 mv are shown. The decrease in \((dV/dt)_{\text{max}}\) was greater at ~66 mv, indicating a shift in the resting potential-\((dV/dt)_{\text{max}}\) curve. The results shown in Figure 2 illustrate the shift of the curve and the dose dependent effect of lidocaine. On the left, the absolute values of \((dV/dt)_{\text{max}}\) are plotted against the resting potential. On the right, the curves have been normalized. The membrane potential associated with a 50% reduction in \((dV/dt)_{\text{max}}\) was ~68 mv before lidocaine, ~71.5 mv after 4 μg/ml of lidocaine, and ~74 mv after 16 μg/ml of lidocaine had been added to the perfusate. Thus, the curve was shifted along the voltage axis in the hyperpolarizing direction, i.e., in the direction of more negative membrane potentials, by 3.5 mv and 6 mv after 4 and 16 μg/ml of lidocaine, respectively, had been added to the perfusate. The results of all of the experiments are shown in Table 1. In six of the
Effects of lidocaine, 6 µg/ml, on (dV/dt) max when the resting membrane potential is −87 mv (top) and −66 mv (bottom). In this and subsequent figures, the action potentials were recorded at the slower sweep speed and the differentiated upstrokes, shown to the right of the action potential, at the faster sweep speed. The value of Δ to the right of each row is the percent change in (dV/dt) max during the control or the lidocaine perfusion. The value of Δ below each column is the percent change in (dV/dt) max associated with the change in resting potential. This decrease was greater during the lidocaine perfusion than it was during the control perfusion.

Effects of 4 and 16 µg/ml of lidocaine HCl on the steady-state relationship between resting membrane potential and (dV/dt) max in a fiber stimulated at 0.2/sec. Absolute values are shown in the graph on the left and normalized values in the graph on the right. Lidocaine caused a dose-dependent decrease in (dV/dt) max at all resting potential levels and shifted the normalized curves along the voltage axis in the direction of more negative membrane potentials.

Effects of Quinidin on the Steady-State Characteristics of (dV/dt) max

Quinidine, like lidocaine, caused a dose-dependent decrease in (dV/dt) max that ranged from 3% to 46% when the resting membrane potential was more negative than −85 mv. However, Figures 4 and 5 show that, unlike lidocaine, the percent decrease in (dV/dt) max was constant at all levels of resting potential. The left section of Figure 5 shows the absolute values of (dV/dt) max . In the right section, the normalized curves show that the percent decrease in (dV/dt) max at any level of resting potential was the same before and after the addition of quinidine. The results of 13 determinations are shown in Table 2. In 9 determinations there was no shift in the normalized (dV/dt) max −resting potential curve. In 4 determinations a 1–2 mv shift of

Weidmann (4) has shown in Purkinje fibers that the changes in (dV/dt) max induced by increasing the potassium (K+) concentration of the perfusate are due to the changes in membrane potential alone. The experiments shown in Figure 3 were performed to determine if the lidocaine-induced shift in the membrane potential−(dV/dt) max relationship (inactivation curve) (Fig. 2) was due to lidocaine alone or to the combined effects of K+ and lidocaine. The left and center sections of Figure 3A show the decrease in resting potential and (dV/dt) max associated with an increase in K+ from 5.4 to 9.4 mM. The right section shows that restoring the resting membrane potential by administering a constant hyperpolarizing current (I) in the presence of the elevated K+ concentration restored (dV/dt) max to its original value. In Figure 3B, the experiment was performed in a fiber perfused with 6 µg/ml of lidocaine. As in Figure 3A, restoration of the resting potential to its original value in the presence of the elevated K+ concentration restored (dV/dt) max . In Figure 3C, the fiber was also perfused with lidocaine-containing solution. In this experiment, the decrease in (dV/dt) max was the same when the resting potential was changed to the same level by increasing the K+ concentration from 5.4 to 9.4 mM (center) or by administering a depolarizing current (right). These experiments confirm Weidmann's observations (4) and show that the shift in the membrane potential−(dV/dt) max relationship induced by lidocaine is independent of the increase in K+ in the perfusate.
the curve along the voltage axis in the direction of more negative membrane potentials was observed.

**EFFECTS OF LIDOCAINE ON THE RECOVERY OF \( (dV/dt)_{\text{max}} \)**

The results of a representative experiment from this series of 13 experiments are shown in Figure 6. In this experiment, the recovery of \( (dV/dt)_{\text{max}} \) was determined at resting potentials of –90 and –79 mv. Both control and lidocaine data could be fitted by monoexponential curves. The arrows indicate the time constants (\( r \)) of the recovery of \( (dV/dt)_{\text{max}} \). Before lidocaine was added, the time constant was 20 msec when the resting potential was –90 mv and 40 msec when the resting membrane potential was –79 mv. This prolongation of the recovery time constant associated with a decrease in resting potential is similar to that previously reported (6). After the addition of 8 \( \mu \)g/ml of lidocaine, the time constant increased to 120 msec when the resting potential was –90 mv and to 180 msec when the resting potential was –79 mv.

The lidocaine-induced prolongation of the time constant of recovery of \( (dV/dt)_{\text{max}} \) was also dose dependent as is illustrated in Figure 7, which shows the results of the 13 experiments. In 5 experiments, the resting potential was held constant and the recovery of \( (dV/dt)_{\text{max}} \) was determined following the addition of two concentrations of lidocaine to the perfusate. The results of these experiments are indicated in Figure 7 by the symbols joined by vertical lines. In 2 experiments (including one of the preceding 5) the time constant was determined at two levels of resting potential without changing the concentration of lidocaine. The results of these experiments are also indicated on the figure by the symbols joined by the diagonal solid lines.

**EFFECTS OF QUINIDINE ON THE RECOVERY OF \( (dV/dt)_{\text{max}} \)**

The results of a representative experiment from this series of 15 experiments are shown in Figure 8. The data shown in this figure were obtained during the continuous impalement of the same fiber from which the lidocaine data shown in Figure 6 were obtained. Figure 8 shows that, although \( (dV/dt)_{\text{max}} \) at each test interval was decreased by quinidine, the time constant of recovery of \( (dV/dt)_{\text{max}} \) was not altered. The results of all 15 experiments are shown in Figure 9. These compiled results indicate that quinidine exerted neither a dose- nor a voltage-dependent effect on the recovery of \( (dV/dt)_{\text{max}} \).

**EFFECTS OF LIDOCAINE AND QUINIDINE ON MEMBRANE RESPONSIVENESS**

The results of the experiments described earlier suggest that the effects of the two drugs on membrane responsiveness, i.e., the membrane potential–\( (dV/dt)_{\text{max}} \) relationship in premature responses initiated during the phase of incomplete repolarization of the preceding action potential (11, 12), differ. We compared the steady-state membrane potential–\( (dV/dt)_{\text{max}} \) relationship to membrane responsiveness curves in three fibers before and after 6 \( \mu \)g/ml of lidocaine had been added to the perfusate and in three other fibers before and after 8 \( \mu \)g/ml of quinidine had been added. In all of the experiments, the basic driving rate was 0.2/sec. Figure 10 shows the effects of lidocaine on these curves; the absolute values are shown on the left and the normalized values on the right. Although the \( (dV/dt)_{\text{max}} \) associated with a membrane potential of –90 mv was depressed only slightly by lidocaine, both the steady-state and the membrane responsiveness curves were shifted along the volt-
FIGURE 3

Oscillographic records from experiments performed to determine whether the increase in K+ concentration shown between A and B and below C contributed to the lidocaine-induced changes in (dV/dt)max. Hyperpolarizing (A and B, right) or depolarizing (C, right) current (I) was introduced in the distal compartment of the sucrose-gap chamber. The current trace was set at the 0-mv line prior to the introduction of the constant current; the magnitude of the current injected is indicated in the right sections of A-C by the deviation of the current trace from this line. The shortening of the action potential duration in A and B (right) and the lengthening in C (right) were caused by the injected current. The lidocaine concentration in B and C was 6 µg/ml.

Discussion

Our study showed that lidocaine and quinidine exert different effects on the steady-state and recovery characteristics of guinea pig ventricular fibers.

LIDOCAINE

Various investigators have shown that lidocaine causes a dose-dependent decrease in (dV/dt)max in atrial, ventricular, and Purkinje fibers (11-13)
EFFECT OF DRUGS ON \((dV/dt)_{max}\)

which is minimal at concentrations below 5 \(\mu g/ml\). Ventricular conduction velocity is slowed slightly in experimental animals (14) but not in man (15, 16). In addition, the QRS complex of the electrocardiogram is not widened by lidocaine (17). Our results were consistent with these reports. We found that lidocaine in concentrations below 10 \(\mu g/ml\) caused less than a 12% decrease in \((dV/dt)_{max}\) when the resting potential was in the range of \(-80\) to \(-90\) mv. However, as shown in Figures 1 and 2 and as previously reported by Singh and Vaughan Williams (13) for atrial and ventricular fibers, the depression of \((dV/dt)_{max}\) became more pronounced when the resting potential was decreased by increasing the extracellular K\(^+\) concentration. Vaughan Williams (18) has attributed this result to a K\(^+\)-induced shift in the lidocaine dose-response curve. Our study showed that this result was due to a lidocaine-induced change in the steady-state relationship between resting membrane potential and \((dV/dt)_{max}\) which became manifest at membrane potentials less negative than \(-80\) mv. We would therefore attribute the effect of the higher K\(^+\) concentration to the associated decrease in resting membrane potential.

The effect of lidocaine on the relationship between \((dV/dt)_{max}\) and membrane potential in premature responses originating from incompletely repolarized fibers, i.e., membrane responsiveness, has been reported only for Purkinje fibers (11, 12). In those experiments, less than 3 \(\mu g/ml\) of lidocaine did not alter or increased slightly the value of \((dV/dt)_{max}\) when the membrane potential prior to depolarization was less negative than the resting potential. At concentrations greater than 3 \(\mu g/ml\), \((dV/dt)_{max}\) was decreased. We showed a similar decrease in membrane responsiveness when the lidocaine concentration was 5 \(\mu g/ml\) or greater. Our results suggest that this decrease can be attributed to the shift in the steady-state relationship between \((dV/dt)_{max}\) and membrane potential, the prolongation of the recovery of \((dV/dt)_{max}\) observed in this study, or both. Of these two factors, the prolongation of recovery appeared to be the more important, since (1) the shift in membrane responsiveness was more pronounced than the shift in the steady-state curve (Fig. 10) and (2) the shift in the steady-state curve did not occur until the resting potential was less negative than \(-80\) mv whereas the shift in membrane responsiveness was apparent at membrane potentials more negative than \(-80\) mv. The prolongation of recovery is probably also responsible for the rate-dependent depression of conduction.
TABLE 2

Effect of Quinidine Gluconate on Steady-State (dV/dt)\textsubscript{max} and on Membrane Potential Associated with a 50% Reduction in (dV/dt)\textsubscript{max}

<table>
<thead>
<tr>
<th>Expt</th>
<th>RMP (mv)</th>
<th>(dV/dt)\textsubscript{max} (v/sec)</th>
<th>MP at 50% (dV/dt)\textsubscript{max} (mv)</th>
<th>Dose (\mu g/ml)</th>
<th>(dV/dt)\textsubscript{max} (v/sec)</th>
<th>Change in (dV/dt)\textsubscript{max} (%)</th>
<th>MP at 50% (dV/dt)\textsubscript{max} (mv)</th>
<th>Shift (mv)</th>
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<tr>
<td>1</td>
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<td>-63</td>
<td>8</td>
<td>201</td>
<td>7</td>
<td>-63</td>
<td>0</td>
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<td>-67</td>
<td>8</td>
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<td>5</td>
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<tr>
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<td>6</td>
<td>310</td>
<td>11</td>
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<td>0</td>
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</table>

Abbreviations are the same as those in Table 1.

Our results suggest that, although lidocaine in concentrations below 5 \mu g/ml may not alter or may depress only slightly the maximum rapid inward current, it does alter the voltage-dependent changes in sodium conductance (20). Such an effect would explain the shift in the steady-state curve even when the maximum (dV/dt)\textsubscript{max} was not depressed. It is probable that in concentrations greater than 5 \mu g/ml lidocaine does decrease the maximum inward current. Such a decrease has been demonstrated in the node of Ranvier (21) and in squid axons (22) and is probably responsible for the decrease in (dV/dt)\textsubscript{max} that occurred when the lidocaine concentration exceeded 5–10 \mu g/ml.

The mechanism whereby lidocaine prolongs the reactivation kinetics of the rapid sodium inward current is not obvious from this study. Slowing of the recovery of (dV/dt)\textsubscript{max} may be due to a direct effect of lidocaine on the reactivation kinetics of the rapid inward current (5) or to the kinetics with which lidocaine itself reacts with its active site, presumably on the inside of the membrane (23).

QUINIDINE

Other investigators have shown that quinidine in concentrations of 10 \mu g/ml or less decreases (dV/dt)\textsubscript{max} in atrial, ventricular, and Purkinje fibers in spontaneously beating preparations or in preparations stimulating at physiological rates (7, 9, 24–27). In addition, quinidine slows intraventricu-
EFFECT OF DRUGS ON $\frac{dV}{dt}$

**Figure 7**

Effect of different concentrations of lidocaine on the time constant ($r$) of recovery of $\frac{dV}{dt}$ at resting membrane potential relationship (13 experiments). Joined symbols indicate experiments in which the recovery of $\frac{dV}{dt}$ was determined for more than one concentration of lidocaine or at more than one level of resting potential.

**Figure 8**

Graphic representation of the effect of quinidine on the recovery of $\frac{dV}{dt}$ at the resting potential of $-90$ mV. The lidocaine data are the same as those shown in Figure 6 at the resting potential of $-90$ mV.

**Figure 9**

Results of 15 experiments in which the effects of quinidine on the recovery of $\frac{dV}{dt}$ were assessed. $r$ = time constant of recovery.

Experimental results shown in Figures 7, 8, and 9.

We were unable to demonstrate any effect of quinidine on the recovery kinetics of $\frac{dV}{dt}$ at any level of membrane potential. Driot and Carnier (30) have reported that quinidine prolongs the recovery of the rapid inward current in voltage-clamped atrial fibers at 19°C. This result is not easily reconciled with our findings. It is possible that species and fiber differences and differences in experimental procedure are responsible for the divergent results. On the basis of our experiments, and contrary to our expectations, we could not attribute the previously reported rate-dependent effect of quinidine in mammalian fibers to a change in reactivation kinetics. Rather, our results suggest that this effect must be due to other factors.

Weidmann (9) has shown that quinidine, like cocaine, decreases $\frac{dV}{dt}$ at all levels of resting potential in Purkinje fibers driven at a rate of 1/sec. We observed similar results in ventricular fibers driven at a rate of 0.2/sec. However, unlike the effect observed with lidocaine, the normalized
Effects of lidocaine on the steady-state relationship between membrane potential and (dV/dt)max (solid lines) and membrane responsiveness (broken lines). The steady-state curves were determined by depolarizing the fiber with KCl. The membrane responsiveness curves were determined by inducing premature responses before the completion of repolarization.

The effect of quinidine on membrane responsiveness has not been reported previously for either Purkinje or ventricular fibers. In our study, membrane responsiveness was depressed by quinidine. However, like the steady-state effect, the depression was constant at all levels of membrane potential, and thus the normalized curves did not change. This result is consistent with the observation that quinidine did not alter the steady-state or recovery characteristics of (dV/dt)max and, coupled with the steady-state results, suggests that quinidine did not alter the membrane potential-dependent conductance variables (20). Our results suggest that the depression of both the steady-state and the membrane responsiveness curves was a manifestation of the rate-dependent effect of quinidine reported by others (7, 8).

Several different schemes for categorizing the various antiarrhythmic drugs have been proposed (1, 2, 33). The drugs have been separated into those having a direct membrane effect (2), a rate-dependent effect (33), or an effect on membrane responsiveness (1). Our results suggest that drugs having these effects can be subdivided into those which alter the steady-state variables, those which alter the kinetic variables, and those which act by some other mechanism. Such subclassification would place quinidine and lidocaine into different categories.

Although our results were obtained at nonphysiological driving rates, it is possible that the differences which we observed may be pertinent to some of the known differences in clinical effects of quinidine and lidocaine. For instance, the ability of quinidine but not of lidocaine to convert atrial fibrillation to normal sinus rhythm and to widen the QRS complex on the electrocardiogram may be due to quinidine's rate-related effect on (dV/dt)max. Our results predict that lidocaine will also exert a rate-dependent effect on (dV/dt)max in depolarized ventricular fibers when the diastolic interval is short enough (approximately 300 msec) to be influenced by the prolonged recovery of (dV/dt)max. Furthermore, our results predict that lidocaine will decrease (dV/dt)max in premature responses without altering this parameter in the nonpremature response, whereas quinidine's effect on (dV/dt)max will occur in both the nonpremature and the premature response. The results of studies designed to test these predictions have been reported in abstract form (34).

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