THE EFFECT of antiarrhythmic drugs on the maximum upstroke velocity (V_{max}) of the cardiac action potential (AP) is generally considered an important factor in the therapeutic actions of such drugs. According to present concepts of excitable membrane function, antiarrhythmic drugs diminish V_{max} by blocking sodium channels. It is, however, quite different for different drugs. Moreover, for any individual agent the drug effect on V_{max} is a complicated function of the experimental conditions, e.g., rate, number of action potentials at any particular rate, extrasystoles and their time relation to the steady driving rate, extracellular potassium concentration and resting membrane potential. Such rate-, voltage- and time-dependent drug interactions with transmembrane channels have also been described for local anesthetics in other excitable tissues.

Recently, we proposed a model, the parameters for which were derived from previously published reports. This model (fig. 1) proposes that antiarrhythmic drugs interact with membrane sodium channels in the rested (R), activated (A) and inactivated (I) states, and that each of these interactions is characterized by an association (k) and dissociation (l) rate constant. The transitions between the rested, activated and inactivated states are governed by standard Hodgkin- and Huxley-type equations, but inactivation parameters of the drug-associated channels are shifted to more negative potentials by an amount ΔV (voltage shift). Finally, we postulate that drug-associated channels do not conduct, even in the activated state; i.e., they are blocked.

The published data used for the original derivation of the model did not extend over the full range of rate and rhythm, and in some cases were available only for the normal resting potential. However, antiarrhythmic drugs are frequently used in tissues exhibiting tachycardias, bradycardias or extrasystoles, and in tissues depolarized by ischemia. We therefore investigated the effects of quinidine and lidocaine on V_{max} over a full range of membrane potentials, extrasystolic recovery intervals and driving rates. A preliminary report has been presented.

**Materials and Methods**

The experimental results were obtained from right ventricular papillary muscles of 14 guinea pigs. The animals were stunned by cervical dislocation and their hearts quickly excised and transferred to a cold salt solution. The preparations were mounted in a threecompartment, single-sucrose-gap chamber in such a way that less than 1 mm of myocardium protruded into the test chamber. The test chamber was perfused at about 10 ml/min with a solution having the following composition (mM): NaCl 145, KCl 4, CaCl\_2 1.8, MgCl\_2 1.1 and glucose 5. The solution was buffered with 5 mM Tris and titrated to a pH of 7.35. The middle compartment was perfused with an isotonic sucrose solution enriched with 0.025 mM CaCl\_2, while the current-injection chamber was perfused with an isotonic KCl solution. All solutions were bubbled with 100% oxygen and the temperature was kept at 36–37°C. The preparations were allowed to equilibrate for at least 1 hour before starting the experiment.

Transmembrane potentials were recorded using
The membrane potential was depolarized by adding aliquots of KCl to the perfusate of the anterior chamber until the desired membrane potential was obtained. Alternatively, hyperpolarization and depolarization were obtained by current injection through the sucrose gap.

Determinations were made before addition of drug, after 30 minutes of equilibration with the agent, and 1 hour after washing out the drug. Lidocaine HCl and quinidine gluconate were used. All data were obtained from single-cell impalements for the duration of the experiments. Only preparations in which the latency (time between the onset of the stimulus and the upstroke of the action potential) was less than 5 msec were accepted in the present study. In addition, all preparations in which $V_{\text{max}}$ varied more than 5% as a function of stimulus strength (1.2–1.5 times threshold) were rejected from the study; 16 of 30 preparations were rejected.

A wide range of drug concentrations was studied, from therapeutic to toxic levels, to obtain the most rigorous possible test of the model. Cumulative doses for both drugs included 2, 4, 8, 16 and 32 µg/ml. In six experiments quinidine was the first and only drug used because it did not readily wash out. In the eight other experiments lidocaine was the first drug. Since all the lidocaine effects could readily be reversed by a washout period, we then superfused the preparations with quinidine.

For the prediction of the drug effects on $V_{\text{max}}$ we used the model equations and parameters described previously and summarized in figure 1. This model computes the predicted sodium conductance ($G_{\text{Na}}$) as being directly proportional to the fraction of channels in the activated (A) state (fig. 1). The model similarly computes the fraction of channels in the other pools using a straightforward set of differential equations. For each simulation in the present study the program was given the membrane potential, drug-rate constants and concentration, and the stimulus pattern. Graphic displays of the predicted $G_{\text{Na}}$ values were compared with the normalized experimentally observed $V_{\text{max}}$ by plotting both sets of data on the same time scale.

**Results**

The decrease of $V_{\text{max}}$ by quinidine or lidocaine is a function of the drug and its concentration, driving rate, time elapsed since the previous action potential (i.e., poststimulation recovery) and the transmembrane potential. Because these factors operate simultaneously, we designed our experiments to isolate the effects of individual variables as shown below.
Driving rate markedly influences the decrease of $V_{\text{max}}$ by both quinidine and lidocaine. However, only steady-state data were available for lidocaine and only one study of the rate of onset of quinidine effects has been published. Because computer simulations using the model predicted a surprising difference between the two drugs in the rate of development of block during a train of action potentials, it was especially important to obtain beat-by-beat $V_{\text{max}}$ data for the two drugs under identical conditions. The predicted $G_{\text{Na}}$ and observed $V_{\text{max}}$ effects of therapeutic concentrations of lidocaine and quinidine during pulse trains at the normal resting potential for several different driving rates are shown in figure 2. At driving rates slower than 0.1 Hz (not shown), and normal transmembrane potential, therapeutic concentrations of the drugs elicit little or no activation-dependent decrease of $V_{\text{max}}$. At fast rates (2 Hz and faster) both drugs decrease steady-state $V_{\text{max}}$ substantially. However, whereas this rate-dependent effect becomes significant at driving rates faster than 0.2 Hz for quinidine, for lidocaine the driving rate must exceed 1 Hz in order for $V_{\text{max}}$ to decrease. The predictions of the rate-dependent drug effects on steady-state $G_{\text{Na}}$ are in good agreement with the experimental $V_{\text{max}}$ results shown. Similar results were obtained in all experiments and these results are comparable to the rate-dependent drug effects described by other laboratories.

As noted above, the model unexpectedly predicted that in the presence of lidocaine, if $G_{\text{Na}}$ declines at all, it should quickly decrease to a quasi-steady level, whereas this steady state should develop rather slowly in the presence of quinidine (compare figures 2H and 2L). Experimentally, this slow, progressive decline for quinidine has been documented previously for a single driving rate; no such data were available for lidocaine at any rate in any cardiac tissue. As shown in figure 2, under all experimental conditions where lidocaine decreased $V_{\text{max}}$, a quasi-steady-state $V_{\text{max}}$ was reached in three or fewer action potentials. This was much faster than for quinidine, in which 20–50 action potentials were required to reach a steady state.

Figures 2L and 3L show that $V_{\text{max}}$ after an initial rapid (one or two action potentials) decline, continued to decline at a much slower rate for the remainder of the train. Similar apparent deviations were frequently observed at fast driving rates in preparations in which the diastolic membrane potential was not controlled. This slow decline of $V_{\text{max}}$ is caused by the slow

![Figure 2](http://circ.ahajournals.org/)

**FIGURE 2.** Comparison of the model-predicted ($G_{\text{Na}}$) and experimentally observed ($V_{\text{max}}$) rate-dependent drug effects. $C = \text{control}; Q = \text{quinidine gluconate} 1.5 \times 10^{-5} \text{M (}8 \mu\text{g/ml); } L = \text{lidocaine hydrochloride} 3 \times 10^{-5} \text{M (}8 \mu\text{g/ml); } B = \text{fraction of sodium channels blocked; } G_{\text{Na}} = \text{model-predicted sodium conductance; } V_{\text{max}} = \text{experimentally observed maximum upstroke velocity of the action potential. Vertical calibration marks: } B = 0-0.5; G_{\text{Na}} = 0-0.5; V_{\text{max}} = 0-150 \text{ V/sec. Horizontal calibration is 10 seconds.}
depolarization of the resting potential that accompanies fast driving rates in guinea pig papillary muscle. Indeed, when the depolarization was included in our computer simulation, it also showed a slight progressive decline of $G_{Na}$ of a magnitude similar to that observed in the experiments. Conversely, if during the experiment the diastolic potential was clamped at its original value, no such additional decline of $V_{\text{max}}$ was observed. We therefore conclude that this slow decline of $V_{\text{max}}$ is solely due to depolarization of the preparation.

The above rate-dependent effects of quinidine and lidocaine are accentuated by depolarization and attenuated by hyperpolarization.

Poststimulation recovery of $V_{\text{max}}$ is another important parameter in characterizing antiarrhythmic drug action. Figure 4 is a comparison of the model predictions of $G_{Na}$ and the experimentally observed poststimulation recovery of $V_{\text{max}}$ in the presence of lidocaine or quinidine at a normal resting potential. Whereas under control conditions recovery of $G_{Na}$ or $V_{\text{max}}$ was complete in a few milliseconds, this process was greatly slowed in the presence of lidocaine or quinidine. Both the model and the experimental results show that poststimulation time to 50% recovery was a few hundred milliseconds for lidocaine and was prolonged to several seconds for quinidine (fig. 4). The experimental results were very similar in all preparations and resembled closely those already published for quinidine and lidocaine.

However, the data of the last two studies cited suggest that poststimulation recovery is a monoeponential process. In contrast, the model predicted that, at least at membrane potentials where part of the blocked channels are in the I' pool and others are in the R' pool, dissociation of the drug from the sodium channels should occur along two pathways, R' to R and I' to I (fig. 1). Since the rate constants of these two dissociation routes are quite different (R' to R is much faster than I' to I), the model predicted that this poststimulation recovery should not necessarily occur with a single time constant, as previously proposed. In the present experiments there appeared to be two processes in the poststimulation recovery of $V_{\text{max}}$: a fast process that was dominant at more negative membrane potentials and a slow one that was dominant at depolarized (less negative than $-80 \text{ mV}$) membrane potentials. At intermediate potentials we could some-

![Figure 3](http://circ.ahajournals.org/figure3.jpg)

**Figure 3.** Comparison of the model-predicted ($G_{Na}$) and experimentally observed ($V_{\text{max}}$) voltage dependence of drug effects. Hyperpolarization and depolarization were elicited by current injection. Abbreviations and calibrations the same as for figure 4. In panel E the asterisk indicates that this panel was obtained at $-108 \text{ mV}$ instead of $-100 \text{ mV}$, because at the former potential the difference between $G_{Na}$ and $V_{\text{max}}$ was maximal (see text).
times observe both simultaneously. We have previously published an example of this for quinidine, and we observed multiple time constants in the poststimulation recovery of $V_{max}$ in four of our present lidocaine experiments. The fast (hyperpolarized) and slow (depolarized) time constants are not always resolved simultaneously in the −80- to −100-mV range probably because the fast recovery process is so much faster than the slow one that it tends to dominate whenever it is present. However, careful adjustment of the membrane potential allows the demonstration of both processes in any single preparation.

The clear poststimulation recovery of $V_{max}$ in the presence of quinidine contrasts with a previous report, and the reason for this discrepancy is anticipated by the proposed model. Two experimental factors in the protocol of Chen et al., according to the model, would minimize such recovery: 1) poststimulation recovery was measured for only a few hundred to 1000 msec, whereas the time constant of this recovery process is several seconds; and 2) since only a small fraction of the channels associates with quinidine per action potential and since the driving rate was slow, i.e., 0.2 Hz (allowing most of the drug to dissociate from the channels), there was little rate-dependent block, and therefore little poststimulation recovery.

Transmembrane potential. The effects of depolarization on antiarrhythmic drug action are very important. However, we could find only two reports of the effects of hyperpolarization on the action of these drugs. Weidmann, in a classic study of quinidine in Purkinje fibers, and Welld and Bigger, in a voltage-clamp study of lidocaine on the same tissue, showed that hyperpolarization resulted in significant reversal of drug-induced block. The previous studies related to steady-state conditions only and no data were available for ventricular myocardium at hyperpolarized potentials.

Figure 3 is a comparison of the model predictions and the experimentally observed effects of quinidine and lidocaine at a fixed rate and dose, but at various resting potentials. For this comparison we chose a fast driving rate (3.3 Hz), because at slower driving rates the drugs have little or no activation-dependent effects at potentials more negative than −90 mV.

Lidocaine simulation at 3.3 Hz indicated that the activation-dependent decrease of $G_{Na}$ should be minimal at potentials more negative than −107 mV, i.e., increase as the membrane potential becomes more

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**Figure 4.** Comparison of the model-predicted ($G_{Na}$) and experimentally observed ($V_{max}$) drug effects on poststimulation recovery. Column headings refer to the interval between the last regular train stimulus and the extrasystole-evoking stimulus. Abbreviations and calibrations are the same as for figure 2, except $Q = quinidine gluconate 3 \times 10^5 M$ (16 µg/ml); $L = lidocaine hydrochloride 6 \times 10^5 M$ (16 µg/ml); $V_{max} = 0$–137 V/sec.
positive and reach 50% at -80 mV. The experimental data of figure 3 (panels I to L) show that at -120 mV lidocaine elicited no activation-dependent decrease of $V_{\text{max}}$. However, at -100 mV a substantial decrease was already present, and it reached 48% at -85 mV. At more positive potentials, $V_{\text{max}}$ declined steeply and the preparation was unable to follow this stimulation rate at -70 mV. These experimental results are thus in good agreement with the model predictions (fig. 3, I to L). Similar results were obtained in all experiments.

For quinidine, the model predicted that at 3.3 Hz, hyperpolarization must exceed -140 mV to prevent any activation-dependent decline of $G_{\text{Na}}$. At -120 mV it was predicted that the activation-dependent decrease of $G_{\text{Na}}$ should be less than 2%, while a decline of 50% was predicted at -98 mV. The experimentally observed effects of quinidine were qualitatively very similar to these predictions, but they were sometimes shifted by a few millivolts toward more negative potentials, especially when hyperpolarizing current was passed. Such a shift is expected, especially in preparations that require relatively large clamping currents. Indeed, when current is passed, the measured potential at the microelectrode tip is the sum of the transmembrane potential and the voltage drop across the extracellular series resistance.23 Because of inward-going rectification, cardiac tissue requires more current to hyperpolarize than to depolarize. Therefore, the measured change in transmembrane potential may be somewhat erroneous, especially during large hyperpolarizing clamps. The largest such deviation we observed occurred in the experiment shown in figure 3. In this experiment the decline of $V_{\text{max}}$ at -120 mV was 8% larger than predicted by the model. The deviation between the predicted $G_{\text{Na}}$ and the observed $V_{\text{max}}$ values was noticeable from -125 to -90 mV and reached a maximum of 23% at -108 mV (see figure 3F). However, this deviation between the model predictions and the experimental results could be accounted for by a 6-mV potential voltage drop across the extracellular series resistance. At -100 mV (not shown) the predicted decline of $G_{\text{Na}}$ was 43%, while the observed decrease of $V_{\text{max}}$ was 54%; the difference between the two was negligible at more positive potentials (fig. 3, G and H). At -73 mV the preparation could no longer follow the stimulation rate. In all experiments the results were similar to the computer predictions: Hyperpolarization attenuated while depolarization accentuated the drug effects on $V_{\text{max}}$.

### Discussion

Antiarrhythmic drugs act by their effects upon automaticity, refractoriness and conduction.1 One important parameter of refactoriness and conduction is the sodium current, which in cardiac tissue can most easily be measured as $V_{\text{max}}$.2 (Refractoriness and conduction are, however, also a function of membrane potential, membrane resistance and threshold potential.)

To compare the predictions of the computer model with the present experimental results, we used the model constants derived from previously published experimental literature.2 The close concordance of the simulation results and the present experimental results suggests that there is considerable homogeneity among experimental preparations of the type used and that the model as formulated readily tolerates minor differences between preparations. Most important, the model can predict drug effects under previously untested conditions.

According to the present results the actions of lidocaine and quinidine on $V_{\text{max}}$ can be described as follows:

**Upstroke of the action potential.** Both drugs have fast interaction rate constants for the activated (open) state (time constants of a fraction of a millisecond), so that during each activation the channels reach approximate equilibrium between the open (A and A', fig. 1) states. Since the affinity of lidocaine for the open channel is much larger than that of quinidine (fig. 1), the fraction of channels that becomes blocked per activation is much larger for lidocaine than for quinidine (figs. 2-4).

**Plateau of the action potential.** The transitions between the inactivated states (I and I', fig. 1) are relatively slow (time constants of several hundred milliseconds for lidocaine and several seconds for quinidine), so that during the short time of the plateau relatively few channels block/unblock under most conditions (figs. 2-4).

**Repolarized action potential.** The drug-free inactivated channels recover (I to R) according to standard Hodgkin-Huxley type kinetics. The drug-associated inactivated channels behave as if the transmembrane potential is decreased by 30-40 mV; similar shifts have been observed for local anesthetics in nerve.12 Therefore, unless hyperpolarized, their recovery (I' to R') is slowed and reduced, while at slightly depolarized membrane potentials recovery is completely prevented. Blocked recovered channels (R') quickly unblock (the R-R' rate constants are fast and the R states have low affinity for the drugs). In contrast, blocked inactivated (I') channels only slowly unblock (see above) or not at all (see below). In this way channels may accumulate in the I' pool, especially at fast heart rates (fig. 2), close extrasystolic coupling intervals (see figure 4) and in depolarized cells (fig. 3). Also, since unblocking from the inactivated state occurs more slowly than for quinidine, quinidine will trap channels at slower driving rates (fig. 2) and for longer coupling intervals (fig. 4) than lidocaine.

Selective depression of depolarized cells has been proposed as an important action of antiarrhythmic drugs.24 The present model provides for at least two important mechanisms for selective depression: 1) since depolarized cells unblock slowly through the I' to I route, whereas more polarized cells can in addition unblock through a much faster route (I' to R' to R), it is clear that at physiologic rates and coupling intervals, the fraction of channels trapped in the I' state will increase with depolarization. 2) In addition to the previous activation-dependent selective depression, lidocaine also possesses a high affinity for the inac-
tivated state. Our discussion will relate to how the effects of antiarrhythmic drugs on the fast inward current may be relevant to conduction in specific arrhythmias. (Clearly these drugs also affect the different outward current channels and autonomic influences, all of which in turn affect automaticity, refractoriness, and conduction.) We assume that antiarrhythmic drugs should degrade conduction in "healthy" tissues as little as possible but preferentially modify the "sick" conduction that causes reentrant arrhythmias in such a way as to abolish arrhythmias. Conduction can be either improved or depressed. Unfortunately, the available antiarrhythmic drugs only reliably depress conduction. It was initially proposed that type II antiarrhythmic drugs could improve conduction, but this has not been confirmed by many investigators.

Premature beats. During diastole the effect of antiarrhythmic drugs on the sodium channels progressively declines. For lidocaine this recovery process is nearly complete in 700 msec, whereas for quinidine little or no recovery occurs during the normal diastolic interval (fig. 3). Thus, while quinidine (2.5 μg/ml) can effectively depress conduction of impulses arising at any time during diastole, lidocaine (5 μg/ml) is mainly effective early in diastole.

The model suggests (fig. 5) that a therapeutic combination of quinidine and lidocaine provides a more effective depression of premature conduction than the equivalent therapeutic concentration of quinidine alone. For this simulation we graphically combined the effects of 5 μg/ml of lidocaine with those of 2.1 μg/ml of quinidine. This combination provides the same depression of the regular beat (1000 msec) as 2.5 μg/ml of quinidine alone. However, it provides considerable extra depression of early extrasystoles. For example, an extrasystole occurring 50 msec after repolarization (dashed line in fig. 5) is depressed 27% by lidocaine (5 μg/ml) alone, 33% by quinidine (2.5 μg/ml) alone, but 52% by the quinidine and lidocaine (2.1 μg/ml plus 5 μg/ml, respectively) combination.

Thus, this combination allows depression of early diastolic conduction to a greater extent than either drug can achieve alone, while not depressing conduction of the regular action potential beyond the depressant action of quinidine alone. This is especially important because therapeutic concentrations of lidocaine are well tolerated even in the presence of high therapeutic concentrations of quinidine.

Results of a preliminary experiment testing this prediction are shown in figure 6. In this experiment, \( V_{\text{max}} \) of the early extrasystole was depressed 13% by lidocaine alone, 25% by quinidine alone, but 79% by the combination of drugs. In contrast, the steady-state (1 Hz) \( V_{\text{max}} \) was depressed by only 35% by the combination of drugs. Because the conditions of this preliminary experiment were not identical to those of the computer simulation we cannot make firm conclusions from the data; however, the prediction of the model appears to be supported. For clinical application, the optimal dose combination of quinidine and lidocaine must be derived from clinical studies, and each patient will probably have to be individually titrated. However, due to its high affinity for depolarized tissue, lidocaine would be expected to be more effective if such tissue is crucial to an arrhythmia. In arrhythmias that do not involve depolarized tissue, quinidine might be expected to be more effective because its action is less voltage-dependent. Finally, the early diastolic extra-depression should not be limited to quinidine and lidocaine, but should be obtainable by combining any "slow" agent with any "fast" agent.

Our results indicate that a model of antiarrhythmic drug action based on a single mechanism of action can predict the effects of both quinidine and lidocaine on \( V_{\text{max}} \) over the full range of driving rates and poststimulation recovery intervals in both normally polarized and depolarized myocardial cells. Many effects predicted by the model were extrapolations into ranges previously not covered experimentally. Moreover, although some of the predictions were

![Figure 5. Computer-predicted effects of therapeutic concentrations of quinidine plus lidocaine on \( V_{\text{max}} \) of extrasystoles. The shaded area indicates the extra depression of extrasystolic \( V_{\text{max}} \) that can be attained by a combination of quinidine and lidocaine. This combination does not cause depression of \( V_{\text{max}} \) of the regular beat beyond that observed in the presence of quinidine alone. This extra depression provides the antiarrhythmic activity necessary to abolish certain reentrant arrhythmias (see Discussion section).](image-url)
somewhat unexpected (e.g., two-beat equilibration for lidocaine; multieponential poststimulation recovery of $V_{\text{max}}$), all were supported by the experimental data. Finally, application of the model can result in clinically testable hypotheses.

Acknowledgment

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Figure 6. Preliminary experimental test of a quinidine-lidocaine combination in guinea pig papillary muscle. Each of the four panels shows an oscilloscope display of a steady-state (1 = $H_1$) action potential with an early extrasystole (nominally 15-msec diastolic interval). At the bottom of each action potential is its upstroke velocity in V/sec (captured in the experiment by a sample-and-hold amplifier and read out in digital form). Upper left: responses in drug-free perfusate. Upper right: responses during superfusion with 6 µg/ml lidocaine. Lower left: responses after washout of lidocaine and exposure to quinidine, 4 µg/ml. Lower right: after adding lidocaine, 6 µg/ml, to the superfusate containing 4 µg/ml quinidine.
Test of a model of antiarrhythmic drug action. Effects of quinidine and lidocaine on myocardial conduction.
L Hondeghem and B G Katzung

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