Evidence for a Specific Receptor Site for Lidocaine, Quinidine, and Bupivacaine Associated with Cardiac Sodium Channels in Guinea Pig Ventricular Myocardium

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SUMMARY. According to the modulated receptor hypothesis, sodium channels have a specific receptor site for local anesthetic and antiarrhythmic drugs. Thus, in the presence of a high concentration of two drugs, competitive displacement of one drug by another may occur. Furthermore, if a drug that has relatively rapid post-stimulation recovery kinetics (e.g., lidocaine) displaces another drug with relatively slow recovery kinetics (i.e., quinidine or bupivacaine), then a net reduction in sodium channel blockade is expected at certain stimulation rates. We tested this prediction, using the maximum upstroke velocity of the ventricular action potential as an indicator of drug-free sodium channels. A single sucrose gap technique was used to stimulate guinea pig papillary muscles, and to control membrane voltage at all times except during the action potential upstroke. Drug-induced inhibition of maximum upstroke velocity increased as the stimulation rate was increased, and was significant (P < 0.05) at stimulation rates between 2.5 and 4 Hz in the presence of 43 nM lidocaine (n = 5), and between 0.15 and 4 Hz in the presence of 3.5 μM bupivacaine (n = 4). The addition of 43 nM lidocaine to a perfusate containing 3.5 μM bupivacaine resulted in a net increase in maximum upstroke velocity that was significant at rates between 1 and 3.3 Hz, with a maximum increase of 25 ± 6% at 1.6 Hz. In contrast, addition of 43 nM lidocaine to a perfusate containing 15 μM quinidine did not result in a significant change in maximum upstroke velocity at driving rates between 0.05 and 3.3 Hz (P > 0.2; n = 4). However, evidence for displacement of quinidine by lidocaine could be demonstrated by measuring post-stimulation recovery after a conditioning train of 19 10-msec pulses applied at 28 Hz. With this stimulation protocol, 41 ± 4% of maximum upstroke velocity recovered slowly from block with a time constant of 3.7 ± 1.2 seconds at −100 mV in the presence of 15 μM quinidine (n = 5). In the presence of a mixture of 43 nM lidocaine and 15 μM quinidine, this slow component was significantly reduced to 16 ± 7% (n = 5; P < 0.01), while 71 ± 13% of maximum upstroke velocity recovered with a time constant of 115 ± 21 msec, typical of lidocaine-blocked channels.

A two-drug version of the modulated receptor theory was formulated. The effects of drug mixtures could be accounted for by this model. Our results provide strong support for the modulated receptor postulate that bupivacaine, quinidine, and lidocaine bind to a common receptor site.

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bupivacaine cardiotoxicity, we investigated the effects of adding lidocaine to a ventricular muscle preparation depressed by bupivacaine. According to the modulated receptor hypothesis, different local anesthetic and antiarrhythmic drugs block sodium channels by binding to a common receptor site (Hille, 1977; Hondeghem and Katzung, 1977). If this is true, then high concentrations of lidocaine (≥20 μM) should be able to bind to and mask a substantial fraction of receptor sites during the upstroke and plateau of the cardiac action potential before bupivacaine binding to inactivated channels can substantially develop. Since lidocaine dissociates more rapidly from the sodium channel receptor during diastole than does bupivacaine (Grant et al., 1980; Clarkson and Hondeghem, 1985), displacement of bupivacaine by lidocaine should result in a net increase in maximum action potential upstroke velocity (Vmax) at normal heart rates (e.g., 1–2 Hz). Such an effect could be beneficial in reducing bupivacaine cardiotoxicity.

In addition to sodium channel block, bupivacaine has a potent negative inotropic effect which may also contribute to its cardiotoxicity (Block and Covino, 1981; Courtney, 1984; Kotelko et al., 1984). Since the inotropic effects of adding lidocaine to a bupivacaine-treated preparation may be of clinical relevance, we also investigated the effect of bupivacaine and lidocaine mixtures on twitch tension.

Finally, to gain further insight into the interaction of two heavily used clinical antiarrhythmics, we also investigated the effects of combinations of lidocaine and quinidine. Since quinidine primarily blocks open channels (Hondeghem and Katzung, 1977; Colatsky, 1982), and dissociation between beats is very slow (time constant of 4–7 seconds) (Grant et al., 1982; Weld et al., 1982), lidocaine should be much less effective in displacing quinidine than it is in displacing bupivacaine.

The test of these predictions should provide further insight into the electrophysiological effects of different drug mixtures, as well as provide a critical test of the hypothesis that local anesthetic and antiarrhythmic drugs block cardiac sodium channels by binding to a common receptor site. A preliminary report of part of this work has been published in a brief communication (Clarkson and Hondeghem, 1984).

**Methods**

**Dissection and Mounting of Muscles**

Guinea pigs of either sex weighing 250–450 g were killed by cervical dislocation. The thorax was opened and hearts were quickly removed. Papillary muscles with a diameter of 0.2–0.8 mm and length of 3.0–5.0 mm were dissected free from the right ventricle and mounted in a tissue bath divided into three chambers (posterior, central, and anterior) by two rubber membranes. The methods used were similar to those used by Beeler and Reuter (1970). Once mounted, the base of the papillary muscle was placed in the posterior chamber, a 2-mm segment in the central chamber, and the tip (less than 0.5 mm long) in the anterior chamber.

**Solutions and Drugs**

The anterior chamber was perfused with a HEPES-buffered salt solution of the following composition (in mM): NaCl, 143; KCl, 4; CaCl2, 1.8; MgCl2, 1.1; d-glucose, 5; and HEPES, 5. The solution was titrated to a pH of 7.38 ± 0.01 with approximately 3 mM NaOH, equilibrated with 100% oxygen, and maintained at 36 ± 0.2°C. The middle chamber was perfused with an isotonic sucrose solution to which glucose (5 mM) and CaCl2 (40 μM) had been added. The posterior chamber was perfused with a HEPES solution similar to that perfusing the anterior chamber, with the exception that all NaCl had been replaced with an equimolar amount of KCl. Drugs (quinidine gluconate, lidocaine hydrochloride, and bupivacaine hydrochloride) were dissolved directly into the HEPES solution perfusing the anterior chamber. After the addition of either lidocaine or bupivacaine, an equilibration period of 30 minutes was allowed for drug effects on Vmax to approach steady state. Since quinidine's effect on Vmax takes somewhat longer to approach steady state, the minimum equilibration period used with this drug was 50 minutes.

**Electrophysiological Techniques**

To measure transmembrane potential, we used conventional glass microelectrodes filled with 3 M KCl and attached them to a high input impedance voltage follower with input capacitance compensation. Current used for stimulation and voltage clamping the tissue in the anterior chamber was applied from the posterior chamber and across the sucrose gap. Command pulses were generated by a microprocessor-based stimulator. Action potential upstrokes were elicited by current pulses, 1 msec long. The intensity of the current pulse was adjusted to maintain a constant latency between the stimulus and the time at which the maximum upstroke velocity (Vmax) of the action potential was achieved. Vmax was measured by electronic differentiation of the action potential upstroke (Hondeghem and Cotner, 1978), and recorded on a Grass model 7 polygraph. During voltage clamp, membrane potential was controlled at all times except during the initial 5 msec of the action potential (the upstroke during which Vmax was measured, and a few milliseconds of plateau) as well as the 20-second rest periods separating successive clamp protocols. Different voltage clamp pulse protocols (illustrated in the insets of Figures 1, 3, and 5) were used to determine the time course of recovery from block, and rate dependence of block.

**Limitations of Methods**

Vmax was used as an indicator of drug-free sodium channels. All results reported in this study were obtained from muscles in which a single impalement was maintained between paired measurements. Furthermore, all muscles had Vmax values of 150–350 V/sec in the absence of drug, and a less than 5% variation in Vmax as stimulus to maximum upstroke velocity latency was varied within a window of 1 msec. There is some controversy as to whether Vmax is linearly related to peak sodium conductance (Cohen and Strichartz, 1977; Hondeghem, 1978; Cohen, 1979; Walton and Fozzard, 1979; Cohen et al., 1984). This controversy can only be resolved when Vmax and peak sodium current have been measured under identical physiological conditions. However, a correct
interpretation of the results of the present study requires only that \( V_{\text{max}} \) be a monotonic function of peak sodium current, so that a decrease in \( V_{\text{max}} \) reflects a decrease in peak sodium current. Recent studies suggest that this is a valid assumption (Walton and Fozzard, 1979, 1983; Bean et al., 1983; Cohen et al., 1984).

**Measurements of Twitch Tension**

Papillary muscles were placed in a single-chambered tissue bath perfused with HEPES-buffered solution. Muscles were stimulated by a pair of bipolar extracellular electrodes placed in the bottom of the bath. The tip of each muscle was attached to a Grass force-displacement transducer by a silk suture (6-0), and the base was fixed to the Sylgard bottom of the bath with several fine pins. Muscles were preloaded to the length at which they developed maximal isometric tension. Before experiments were begun, muscles were paced at 0.5 Hz for 30 minutes to allow them to stabilize. During each experiment, papillary muscles were driven at stimulation rates between 0.2 and 3 Hz. After a change in stimulation rate, measurements were taken when twitch tension had reached steady state. This usually required about 2 minutes.

**Data Analysis**

The time course of recovery from block was defined using a least-square-error nonlinear exponential-fitting routine. To determine whether a single or double exponential function provided a better fit, we fit the data by both a single exponential function (of the form: \( y = A \exp[-t/r] + B \)) and a double exponential function (of the form: \( y = A \exp[-t/r] + B \exp[-t/r] + C \)). The double exponential fit was accepted as the fit of choice whenever it had a mean square error that was at least one-third that obtained with a single exponential.

\( V_{\text{max}} \) values are expressed as either a fraction or percentage of control \( V_{\text{max}} \) at 0.05 Hz. Paired comparisons were evaluated for statistical significance using Student's t-test. Comparisons between more than two groups were evaluated by one-way analysis of variance (ANOVA) and Scheffe's test for critical difference. Differences were considered significant if values of \( P < 0.05 \) were obtained. Results are represented as mean ± SEM.

**Modeling**

The modulated receptor model (Hondeghem and Katzung, 1977) was expanded to describe the effects of a mixture of two drugs. The differential equations for this drug-mixture model are shown in Table 2. The parameters for lidocaine and quinidine are similar to those estimated by Hondeghem and Katzung (1977). However, a few of the parameters were changed in order to provide an adequate fit of the effects of individual drugs in the present experiments. No systematic attempt was made to determine whether other parameter values could fit the data equally well (or better). Simulation of the time course of block during a single action potential required about 3 minutes of computer time.

**Results**

**Effects of Lidocaine, Quinidine, and Bupivacaine on \( V_{\text{max}} \)**

Before investigating the effects of drug mixture, we first determined what drug concentrations would produce a substantial level of block during a train of pulses at a high rate (3.3 Hz), as well as the relative rates of recovery from block at normal diastolic potentials (e.g., \(-85 \text{ mV}\)). Pacing a papillary muscle at 3.3 Hz under control conditions resulted in only a small reduction of \( V_{\text{max}} \) (Fig. 1A) which may be largely ascribed to accumulation of slow inactivation (Saikawa and Carmeliet, 1982; Clarkson et al., 1984). However, in the presence of either bupivacaine (3.5 \( \mu \text{M} \)), lidocaine (43 \( \mu \text{M} \)), or quinidine (15 \( \mu \text{M} \)), the same pulse pattern resulted in a marked use-dependent accumulation of block which approached a steady state level by the end of a 19-beat pulse train (Fig. 1A). This steady state level of block results from the fact that block development during each action potential is approximately equal to the amount of recovery from block which occurs between each beat. The accumulated block slowly dissipated, after this pulse train, if the muscle was allowed to rest (Fig. 1B). In the absence of drug, \( V_{\text{max}} \) recovers from inactivation with an exponential time course having a time constant of less than 30 msec at \(-85 \text{ mV}\) (Gettes and Reuter, 1974) (Fig. 1B). In the presence of drug, an additional slower exponential component representing recovery of drug-blocked channels can be observed. The time constant of this recovery process is different for channels blocked by different drugs (see Fig. 1B). At \(-85 \text{ mV}\), channels blocked by lidocaine recover with a time constant of 184 ± 17 msec (\( n = 6 \)), channels blocked by bupivacaine recover with a time constant of 1.1 ± 0.2 seconds (\( n = 5 \)), and channels blocked by quinidine recover with a time constant of 4.0 ± 0.8 seconds (\( n = 4 \)). Characterization of the time course of recovery of drug-blocked channels and extrapolation of this process back to zero time (the y-intercept) provides an estimate of the fraction of channels blocked by drug at the end of the conditioning train (Khodorov et al., 1976; Bean et al., 1983). Using a least-squares fit of the time course of \( V_{\text{max}} \) recovery, we estimated the level of use-dependent block at the end of the 19th beat to be 63 ± 4% (\( n = 5 \)) in the presence of 3.5 \( \mu \text{M} \) bupivacaine, 82 ± 7% in 43 \( \mu \text{M} \) lidocaine (\( n = 6 \)), and 51 ± 8% in 15 \( \mu \text{M} \) quinidine (\( n = 4 \)). The fast component representing recovery of drug-free channels from inactivation was not measurable in the presence of 43 \( \mu \text{M} \) lidocaine, since virtually all channels were blocked by drug, and was usually ignored when defining the time course of recovery in the presence of bupivacaine or quinidine by measuring \( V_{\text{max}} \) only after a recovery interval greater than 100 msec.

**Effects of Mixing Lidocaine and Bupivacaine**

**Rate-Dependent Effects on \( V_{\text{max}} \)**

To determine the effects of drugs and drug mixtures on \( V_{\text{max}} \) at steady state at different stimulation rates, we clamped the action potential plateau to +20 mV for 180 msec at all stimulation rates, and clamped the diastolic potential to \(-85 \text{ mV}\) (as illustrated in Fig. 1A). In the presence of 3.5 \( \mu \text{M} \) bupi-
vacaine alone, the steady state level of $V_{\text{max}}$ decreased progressively as the stimulation rate was increased from 0.05 to 4 Hz (Fig. 2). This decrease was significant at all stimulation rates between 0.15 and 4 Hz ($P < 0.01$). Lidocaine (43 μM) also reduced $V_{\text{max}}$ in a rate-dependent manner, but this reduction was significant only at stimulation rates between 2.5 and 4 Hz ($P < 0.05$). In addition, the extent of $V_{\text{max}}$ reduction by lidocaine was significantly less than that produced by bupivacaine at all rates below 4 Hz ($P < 0.05$).

In four experiments, switching the superfusate solution from one containing 3.5 μM bupivacaine to one containing a mixture of 3.5 μM bupivacaine and 43 μM lidocaine resulted in a significant net increase in $V_{\text{max}}$ (reduction of block) at stimulation rates between 1 and 3.3 Hz ($P < 0.05$) (see Fig. 2). The net increase in $V_{\text{max}}$ was maximal at 1.67 Hz (100 beats/min), where addition of lidocaine resulted in an increase of $V_{\text{max}}$ from 57 ± 3% to 82 ± 3% of control $V_{\text{max}}$ ($P < 0.02$; $n = 4$). The level of $V_{\text{max}}$ block in the presence of a mixture of 43 μM lidocaine and 3.5 μM bupivacaine was not significantly different than that obtained in 43 μM lidocaine alone, over a range of stimulation rates of 0.015 to 4 Hz ($P > 0.3$, one-way ANOVA) (see Fig. 2).

The effect of mixing lower concentrations of lidocaine (13 or 21 μM) with 3.5 μM bupivacaine were also determined in two additional experiments. The effects were qualitatively similar to those obtained with 43 μM lidocaine, except that the net increase in $V_{\text{max}}$ was smaller. For example, the net increase in $V_{\text{max}}$ at 1.6 Hz 30 minutes after we had switched from a bupivacaine perfusate to a perfusate containing a mixture of bupivacaine and lidocaine, was 9% when 13 μM lidocaine was used, and 12% with 21 μM lidocaine, compared to 25% with 43 μM lidocaine.

**Recovery Kinetics**

To determine whether the change in $V_{\text{max}}$ observed upon addition of lidocaine to a bupivacaine-depressed preparation resulted from a reduction in bupivacaine-blocked channels, we characterized the
time course of recovery from use-dependent block. In the presence of a mixture of 43 μM lidocaine and 3.5 μM bupivacaine, recovery from block contained two definable exponential components (Fig. 3). The fast component (83 ± 5% of control \(V_{\text{max}}\)) had a time constant of 179 ± 40 msec \((n = 5)\). Neither the amplitude nor the time constant of the fast component was significantly different from that obtained in the presence of 43 μM lidocaine alone \((P > 0.7)\). The slow component had a time constant of 1.2 ± 0.1 seconds \((n = 5)\), and was not significantly different from that obtained in the presence of bupivacaine alone \((P > 0.7)\). However, the amplitude of the slow component \((11 ± 6%\) of control \(V_{\text{max}}\)) was significantly smaller than that obtained in the presence of bupivacaine alone \((63 ± 4%)\) \((P < 0.001; n = 5)\).

**Contractility**

In the presence of bupivacaine alone, twitch tension was significantly reduced at stimulation rates between 0.2 and 3 Hz (Table 1). However, the negative inotropic effect of bupivacaine was not significantly rate-dependent over this range of stimulation rates \((P > 0.10, \text{one-way ANOVA})\), in marked contrast to its effect on \(V_{\text{max}}\) (compare Table 1 and Fig. 2). Addition of lidocaine did not result in a significant change in twitch tension at stimulation rates between 0.2 and 0.5 Hz (see Table 1). However, addition of lidocaine did result in a significant further decrease in twitch tension at 1 and 2 Hz \((P < 0.02)\). Thus, lidocaine does not reduce bupiva-

**Table 1**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Stimulation rate (Hz)</th>
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<tr>
<td></td>
<td>0.2</td>
</tr>
<tr>
<td>3.5 μM Bupivacaine</td>
<td></td>
</tr>
<tr>
<td>((n))</td>
<td>63 ± 14</td>
</tr>
<tr>
<td></td>
<td>(4)</td>
</tr>
<tr>
<td>3.5 μM Bupivacaine +</td>
<td></td>
</tr>
<tr>
<td>43 μM lidocaine ((n))</td>
<td>54 ± 6</td>
</tr>
<tr>
<td></td>
<td>(3)</td>
</tr>
</tbody>
</table>

* Twitch tension expressed as percent of control (mean ± SEM).
† Bupivacaine reduction of twitch tension was not significantly different at different stimulation rates \((P > 0.6; \text{one-way ANOVA})\).
‡ Significant additional depression after lidocaine was added to bupivacaine \((P < 0.02; \text{Scheffe's test})\).
quinidine's depressive effect on contractility, in contrast to its ability to attenuate bupivacaine's effect on $V_{\text{max}}$.

Effects of Mixing Lidocaine and Quinidine

Steady State $V_{\text{max}}$

Quinidine (15 µM) progressively reduced $V_{\text{max}}$ in a rate-dependent manner as the stimulation rate was increased from 0.05 to 3.3 Hz (see Fig. 4). However, addition of 43 µM lidocaine to the quinidine perfusate did not significantly affect the steady state $V_{\text{max}}$ obtained at rates between 0.5 and 3.3 Hz ($P > 0.2$) (Fig. 4).

Recovery Kinetics

Quinidine's ability to block open sodium channels rapidly during the action potential upstroke, in combination with its slow rate of dissociation between beats (i.e., similar to an 'irreversible antagonist'), may make quinidine difficult to displace. To provide more favorable conditions for observing reduction of quinidine block by lidocaine, we used a conditioning train of 19 10-msec pulses (5 msec for latency and upstroke followed by 5 msec at +20 mV). Each pulse was separated by a diastolic interval of 25 msec at −100 mV (illustrated in Fig. 5). This pulse protocol was designed to minimize dissociation of lidocaine-blocked channels between beats, yet provide nearly complete recovery from fast inactivation of drug-free channels, and negligible accumulation of slow inactivation (Clarkson et al., 1984). In the presence of 15 µM quinidine alone, 41 ± 4% of control $V_{\text{max}}$ recovered with a time constant of 3.7 ± 1.2 seconds at −100 mV following this rapid pulse train ($n = 5$). In the presence of a mixture of 43 µM lidocaine and 15 µM quinidine, recovery from block contained two definable components (Fig. 5). One component (71 ± 13% of control $V_{\text{max}}$) had a time constant of 115 ± 21 msec, and probably reflects recovery of lidocaine-blocked channels ($n = 5$). The other component had a time constant of 3.0 ± 0.7 seconds ($n = 5$), which was not significantly different from that observed in the presence of quinidine alone ($P > 0.5$). However, the amplitude of the slow component in the presence of the lidocaine-quinidine drug mixture was significantly reduced from 41 ± 4% to 16 ± 7% of control $V_{\text{max}}$ ($P < 0.01; n = 5$) (see Fig. 5).

Discussion

Evidence for a Specific Drug Receptor

Our results clearly demonstrate that lidocaine can, under certain conditions, reduce the fraction of sodium channels blocked by either bupivacaine or quinidine. These results indicate that one drug can displace another from its site of action, and suggests that local anesthetic and antiarrhythmic drugs exert their effects by binding to a common receptor site (Hille, 1977; Hondeghem and Katzung, 1977). Evidence for competitive interactions between different local anesthetic drugs has also been recently obtained in nerve tissue (Rimmel et al., 1978; Schmidt- mayer and Ulbricht, 1980; Pichon et al., 1981). This evidence for competitive drug interactions and displacement also provides strong evidence against hypotheses which propose that local anesthetic and antiarrhythmic drugs block sodium channels by a nonspecific effect on the cell membrane (Seeman, 1972; Lee, 1976). Unless there is a saturable receptor
TABLE 2

<table>
<thead>
<tr>
<th>Drug</th>
<th>Bupivacaine</th>
<th>Lidocaine</th>
<th>Quinidine</th>
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<tr>
<td>$k_R$ (per msec)</td>
<td>500</td>
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<td>0</td>
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<tr>
<td>$l_R$ (per msec)</td>
<td>1</td>
<td>1</td>
<td>0.05</td>
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<tr>
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<td>1</td>
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<td>12,000</td>
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<td>2</td>
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</tr>
<tr>
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<td>0.02</td>
<td>0.000154</td>
</tr>
<tr>
<td>$\Delta V_i$ (mV)</td>
<td>28</td>
<td>35</td>
<td>48</td>
</tr>
</tbody>
</table>

*Drug-induced voltage shift of inactivation.*

![Figure 6](image)

**FIGURE 6.** A schematic diagram of the two-drug mixture version of the modulated receptor model. Drug-free states of the sodium channel are indicated by R (rested), O (open), and I (inactivated). Transitions between these three states are governed by Hodgkin-Huxley rate constants (HH). Drugs $D_1$ and $D_2$ may bind to each drug-free state with different rate constants $k_{R1}$, $k_{O1}$, $k_{O2}$, $k_{I1}$, $k_{I2}$ and $k_{R2}$ indicate drug association rate constants, while $l_{R1}$, $l_{O1}$, $l_{O2}$, $l_{I1}$, and $l_{I2}$ represent drug dissociation rate constants. The voltage dependence for inactivation of drug-associated (blocked) states are shifted to more negative potentials by an amount $\Delta V_i$ or $\Delta V_o$, resulting in different rate constants $HH'$ and $HH''$. For further discussion, see Appendix, and Hondeghem and Katzung (1977).

To test the ability of the model to predict displacement of bupivacaine and quinidine by lidocaine, we computed state-dependent rate constants and voltage shifts which could well describe the effect of each drug alone (see Table 2 and Fig. 7). Using these parameters and the drug-mixture model, we then simulated the predicted outcome of mixing lidocaine with either bupivacaine or quinidine. As shown in Figure 7, the model simulations (solid curves) have time courses very similar to the dashed curves which represent the time courses predicted from the exper-

![Figure 7](image)

**FIGURE 7.** Post-stimulation recovery of $V_{max}$ in the presence of drug and drug mixtures. The dashed lines represent the time course of $V_{max}$ recovery estimated from the mean experimental data (time constants and amplitudes), and the solid lines indicate the time course of $V_{max}$ predicted by the model using the rate constants and voltage shifts shown in Table 2. Part A shows the time course of $V_{max}$ recovery at $-85$ mV after a 19-beat train of action potentials at 3.3 Hz. The action potential duration was 185 msec. $L = 43 \mu M$ lidocaine, $B = 3.5 \mu M$ bupivacaine. Part B shows the time course of $V_{max}$ recovery at $-100$ mV after a 19-beat train of action potentials at 28 Hz. The action potential duration was 10 msec. $L = 43 \mu M$ lidocaine, $Q = 15 \mu M$ quinidine.
The modulated receptor hypothesis may be a useful tool for predicting the electrophysiological effects of drug mixtures. In a beating heart, drug-receptor interactions do not typically achieve equilibrium, but rather change dynamically throughout the cardiac cycle. During an action potential, sodium channels cycle through a minimum of three different states (rested, open, and inactivated). Most local anesthetic and antiarrhythmic agents have a very low affinity for the receptor site when the channel is in the rested state, but have a high affinity for the receptor when the channel is open or inactivated (Hondeghem and Katzung, 1984). Consequently, block develops during each action potential, and then dissipates when the channels return to the rested state at the beginning of diastole. For many drugs (e.g., quinidine and bupivacaine), the rate of drug dissociation is slow enough so that block does not fully dissipate between beats even at very slow heart rates (e.g., 1 Hz).

In the presence of a mixture of two drugs, each drug will compete for a limited number of receptor sites during each action potential. When drug concentrations are very low, mixing two drugs is expected to result in more block than is produced by either drug alone, since the probability that two drugs will attempt to interact simultaneously with the same receptor is relatively low. However, when drug concentrations are raised to levels at which each drug is capable of binding to a large fraction of channels, then each of the two drugs will progressively interfere with the other’s binding. If both drugs have similar affinities for different sodium channel states, as well as similar rates of binding and dissociation, then the competition between the drugs will be of little electrophysiological consequence. However, if one drug has substantially different characteristics, e.g., much faster kinetics for diastolic recovery from block, then the competitive interactions may become quite noticeable at certain driving rates. This is illustrated by the effect of adding lidocaine to a bupivacaine-depressed preparation. Displacement of bupivacaine by lidocaine will result in a progressively larger fraction of channels becoming free from block between beats. The model predicts that at slow stimulation rates the fraction of channels blocked by bupivacaine will be small, and hence there can be relatively little improvement in \( V_{\text{max}} \) due to displacement (see Fig. 2). However, as the driving rate is increased, block by bupivacaine increases, and the addition of lidocaine will therefore result in a larger amount of displacement, and subsequent increase in \( V_{\text{max}} \). At even faster rates (e.g., \( >3 \) Hz), the diastolic interval between beats will not be long enough for block by lidocaine to dissipate. Thus, although fewer channels may be blocked by bupivacaine, a net increase in \( V_{\text{max}} \) will not be observed because of the rate-dependent block by lidocaine.

The time dependence and state dependence of drug-channel interaction appear to be important factors which can influence drug interactions. For example, lidocaine can bind to both open and inactivated channels (Hondeghem and Katzung, 1977; Hondeghem and Matsubara, 1984), in contrast to bupivacaine, which almost exclusively binds to inactivated channels (Clarkson and Hondeghem, 1985). High concentrations of lidocaine (e.g., 43 \( \mu \)M) will sequester a very large fraction of sodium channel receptors during the upstroke of the action potential and early during the plateau, prior to the time that bupivacaine binding (at concentrations \( \leq 3.5 \) \( \mu \)M) can become appreciable (Clarkson and Hondeghem, 1985). These factors give lidocaine a distinct advantage in competing against bupivacaine.

In contrast to bupivacaine, quinidine avidly binds to open sodium channels (Colatsky, 1982; Weld et al., 1982; Hondeghem and Matsubara, 1984). As a result, lidocaine will have to compete with quinidine for available receptors during the upstroke. In addition, quinidine dissociates from its receptor very slowly at normal diastolic potentials (\( r = 4 – 7 \) seconds) (Grant et al., 1982; Weld et al., 1982). Consequently, this drug will be difficult to displace, since there is little cycling between drug-free and quinidine-associated states at normal heart rates. This can account for lidocaine’s inability to significantly alter steady state \( V_{\text{max}} \) in preparations depressed by 15 \( \mu \)M quinidine (see Fig. 4).

Bupivacaine’s Negative Inotropic Effect is Neither Rate Dependent nor Reversed by Lidocaine

The mechanism underlying bupivacaine’s negative inotropic effect is not clear. Possible mechanisms include: reduction of calcium influx due to calcium channel blockade (Eisner et al., 1979), reduction of calcium influx due to shortening of action potential duration (Gibbons and Fozzard, 1971; Ten Eick et al., 1976), inhibition of calcium efflux from the sarcoplasmic reticulum (Herbette et al., 1982), or reduction of intracellular calcium due to reduced intracellular sodium activity and the Na-Ca exchange mechanism (Lee et al., 1980; Eisner et al., 1981; Daut, 1982; Wasserstrom, 1983; Im and Lee, 1984).

The finding that bupivacaine’s negative inotropic effect is not strongly rate dependent (Table 1), in contrast to its effect on \( V_{\text{max}} \) (Fig. 2), suggests that
this drug does not exert its negative inotropic by reduction of sodium ion influx alone. The observation that lidocaine increased \( V_{\text{max}} \) in the presence of bupivacaine without reversing bupivacaine’s negative inotropic effect is also consistent with this hypothesis. However, since we did not voltage clamp the action potential plateau during the contractility experiments, we cannot rule out the possibility that a partial reversal of bupivacaine’s negative inotropic effect attributable to increased sodium ion influx by lidocaine was not attenuated by a lidocaine-induced shortening of the action potential duration.

**Clinical Implications**

The above-described drug interactions of lidocaine and quinidine have two possible clinical implications. First, lidocaine is not expected to be very effective in improving conduction in cardiac tissue that is severely depressed by quinidine. This does not, of course, rule out the possibility that lidocaine could have beneficial effects due to mechanism(s) other than drug displacement (e.g., lidocaine-induced decrease of ectopic pacemaker automaticity). Second, even though lidocaine may not be able to effect steady state \( V_{\text{max}} \) substantially, in the presence of a high concentration of quinidine, it can nevertheless provide an extra depression of early extrasystoles by blocking those channels that are not occupied by quinidine. This has been demonstrated in vitro by Hondeghem and Katzung (1980) and Moyer and Hondeghem (1980). The beneficial effects of combining antiarrhythmic drugs having slow and rapid recovery kinetics for suppression of extrasystoles has also been verified in two clinical studies (Breithardt et al., 1981; Duff et al., 1983).

Bupivacaine cardiotoxicity can be a serious and even lethal clinical condition (Allbright, 1979; Food and Drug Administration, 1983). Signs of bupivacaine cardiotoxicity commonly include signs of depressed conduction (Kotelko et al., 1984). Consequently, therapeutic maneuvers which result in improved cardiac conduction may be beneficial in reducing bupivacaine cardiotoxicity.

Lidocaine appears quite effective in improving \( V_{\text{max}} \) when it is depressed by excessive bupivacaine concentrations in vitro. More important, this reversal of \( V_{\text{max}} \) appears to be maximal at clinically relevant heart rates (1–2 Hz or 60–120 beats/min) (see Fig. 2). These results suggest that lidocaine might be effective in treating bupivacaine-induced arrhythmias that result from slow intraventricular or intratrical conduction. In support of this hypothesis, two recent reports have demonstrated that administration of lidocaine can be effective in terminating bupivacaine-induced arrhythmias in both cats (deJong and Davis, 1981) and man (Davis and deJong, 1982). Whereas the results of this study, as well as those of deJong and Davis, appear to provide a strong experimental basis for the use of lidocaine in treating bupivacaine cardiotoxicity, there are several questions that need to be answered. For example, intravenous administration of lidocaine could conceivably displace bupivacaine bound to plasma proteins (Gohneim and Pandya, 1974), and thereby worsen toxicity. Second, our contractility results suggest that lidocaine does not reduce bupivacaine’s negative inotropic effect, and in high concentrations may further depress contractility (see Table 1). It is not yet clear to what extent the depression of contractility (pump failure) may contribute to bupivacaine mortality. Finally, although therapeutic levels of lidocaine (13–21 \( \mu \)M) produce a measurable increase in \( V_{\text{max}} \) in cardiac tissue depressed by a toxic concentration of bupivacaine (3.5 \( \mu \)M), it is not clear that the increase in \( V_{\text{max}} \) (cardiac conduction) produced by therapeutic concentrations of lidocaine is large enough to produce a beneficial therapeutic effect. Thus, further studies must be performed to determine whether lidocaine is an effective or safe treatment for bupivacaine cardiotoxicity.

**Appendix**

In the drug-mixture version of the modulated receptor hypothesis (illustrated in Fig. 6), the total population of sodium channels is set equal to one:

\[
R + O + I + RD_1 + OD_1 + ID_1 + RD_2 + OD_2 + ID_2 = 1.
\]

There are three major channel pools, a drug-free pool and pools blocked by either drug \( D_1 \) or \( D_2 \). The fraction of channels in the drug-free pool is given by the sum of:

\[
R + O + I,
\]

and the two drug-blocked pools (\( B_1 \) and \( B_2 \)) are given by:

\[
B_1 = RD_1 + OD_1 + ID_1, \\
B_2 = RD_2 + OD_2 + ID_2.
\]

The total fraction of all drug-blocked channels is:

\[
B_T = B_1 + B_2.
\]

If activation is described by the standard \( m^* \) variable, and absence of inactivation for drug-free and drug-associated channels is represented by \( h, h_1', \) and \( h_2' \), then the following equations hold:

\[
R = h - O, \\
RD_1 = h_1' - OD_1, \\
RD_2 = h_2' - OD_2, \\
O = m^*h, \\
OD_1 = m^*h_1', \\
OD_2 = m^*h_2', \\
I = 1 - B_T - h, \\
ID_1 = B_1 - h_1', \\
ID_2 = B_2 - h_2'.
\]

Based upon the association and dissociation rate constants shown in Figure 6, the rate of change in...
B R can be described by the following differential equation:

\[ \frac{dR}{dt} = (k_1 \cdot R + k_{01} \cdot O + k_{11} \cdot I) \cdot [D_1] \\
+ (k_{21} \cdot R + k_{02} \cdot O + k_{22} \cdot I) \cdot [D_2] \\
- (RRI \cdot RD_1 + I_{01} \cdot OD_1 + I_{11} \cdot ID_1) \\
- (RRI \cdot RD_2 + I_{02} \cdot OD_2 + I_{12} \cdot ID_2). \]

The activation parameter 'm' is described in the conventional fashion:

\[ \frac{dm}{dt} = \alpha_m(1 - m) - \beta_m \]

where \( \alpha_m \) and \( \beta_m \) are voltage-dependent functions:

\[ \alpha_m = f_3(V) \]
\[ \beta_m = f_4(V). \]

The functions \( f_3(V) \) and \( f_4(V) \) can be found in Hondeghem and Katzung (1977). The inactivation parameters can also be defined by a set of differential equations:

\[ \frac{dh}{dt} = \alpha_h \cdot 1 + R_{11} \cdot RD_1 + R_{21} \cdot RD_2 + I_{01} \cdot OD_1 + I_{02} \cdot OD_2 - \beta_h \cdot (R + O) - (k_{31} \cdot R + k_{01} \cdot O) \cdot [D_1] - (k_{32} \cdot R + k_{02} \cdot O) \cdot [D_2] \]

\[ \frac{dh}{dt} = \alpha_h' \cdot 1 + (k_{31} \cdot RD_1 + k_{01} \cdot OD_1) \cdot [D_1] \]
\[ - \beta_h' \cdot (RD_1 + OD_1) - (k_{31} \cdot RD_1 + k_{01} \cdot OD_1) \]
\[ \frac{dh}{dt} = \alpha_h' \cdot 1 + (k_{32} \cdot RD_2 + k_{02} \cdot OD_2) \cdot [D_2] - \beta_h' \cdot (RD_2 + OD_2) - (k_{32} \cdot RD_2 + k_{02} \cdot OD_2), \]

where \( \alpha_h \) and \( \beta_h \) are voltage-dependent functions defined by Hondeghem and Katzung (1977):

\[ \alpha_h = f_3(V) \]
\[ \beta_h = f_4(V). \]

and \( \alpha_{h1}, \alpha_{h2}, \beta_{h1}, \) and \( \beta_{h2} \) are identical voltage-dependent functions, but shifted along the voltage axis by an amount \( \Delta V_1 \) or \( \Delta V_2 \), i.e.:

\[ \alpha_{h1} = f_3(V + \Delta V_1) \]
\[ \alpha_{h2} = f_3(V + \Delta V_2) \]
\[ \beta_{h1} = f_4(V + \Delta V_1) \]
\[ \beta_{h2} = f_4(V + \Delta V_2). \]

The functions \( f_3(V) \) and \( f_4(V) \) are the same as those defined by Hondeghem and Katzung (1977).

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