Electrophysiological Effects of the Optical Isomers of Disopyramide and Quinidine in the Dog

Dependence on Stereochemistry

MICHAEL J. MIRRO, AUGUST M. WATANABE, AND JOHN C. BAILEY

SUMMARY We studied the electrophysiological effects of the optical isomers of disopyramide and quinidine on canine cardiac Purkinje fibers. Conventional microelectrode techniques were employed to study the effects of racemic disopyramide, (+)-disopyramide, (-)-disopyramide, quinidine, and quinine. Racemic disopyramide, (+)-disopyramide, and quinidine prolonged action potential duration (APD) measured at 90% repolarization. In contrast, (-)-disopyramide and quinine shortened APD. These directionally opposite effects on repolarization were observed throughout 60 minutes exposure to drug and were concentration-dependent. All five compounds reduced dV/dt of phase 0, increased conduction time, and increased the current requirement for all-or-none depolarization. The effects of all five compounds on dV/dt, conduction time, and current requirements were time- and concentration-dependent. Our results indicate that the stereochromical configurations of disopyramide and quinidine determine their effects on repolarization of cardiac Purkinje fibers. Circ Res 48: 867-874, 1981

THE antiarrhythmic agents, disopyramide and quinidine, possess similar electrophysiological properties in animals and humans. Clinical electrophysiological studies have demonstrated that both compounds prolong His-Purkinje conduction and, in the absence of cholinergic influence, prolong atrioventricular (AV) node refractoriness (Josephson et al., 1973; Lau and Damato et al., 1974; Birkhead and Vaughan Williams, 1977). Microelectrode studies have shown that both agents depress the maximum rate of depolarization, increases conduction time, and prolong the terminal phase of repolarization (Hoffman, 1958; Chen et al., 1975; Kus and Sasy-niak, 1975; and Danilo et al., 1977). Since both disopyramide and quinidine have qualitatively similar electrophysiological effects, numerous investigators have speculated that these two drugs may exert similar antiarrhythmic drug actions (Hauswirth and Singh, 1979).

It has been postulated that the effect of disopyramide and quinidine on the maximum rate of depolarization of cardiac cells is due to inhibition of transsarcolemmal sodium conductance through specific membrane ionic channels, i.e., "fast" sodium channels (Weidmann, 1955; Hauswirth and Singh, 1979). Recent reports suggest that these compounds, as well as other local anesthetics, modify the time- and voltage-dependent fast inward current. The charged molecules are thought to interact with these sites to restrict transmembrane sodium conductance, resulting in attenuation of the upstroke velocity of phase 0 of the cardiac transmembrane action potential.

The binding of pharmacological compounds to specific membrane receptor sites can be influenced by their stereochromical properties. For example, the (-) optical isomer of propranolol is approximately 100 times more potent than the (+) optical isomer at inhibiting the binding of catecholamines to cardiac beta-adrenergic receptors (Alexander et al., 1975). Although propranolol possesses stereospecific beta-adrenergic blocking properties, racemic propranolol and the optical stereoisomers are equipotent in attenuating the maximum rate of depolarization and action potential amplitude of cardiac Purkinje fibers (Coltart and Meldrum, 1971). Thus, the effects of propranolol on the fast inward current are not determined by the stereochromical properties of this compound. In contrast, the slow inward current blocking agents, verapamil and D-600, exert stereospecific effects on both the fast sodium current and the slow calcium current (Bayer et al., 1975; Ehara and Kaufman, 1978). The (+) optical isomers exert potent inhibitory effects on the fast inward current, whereas the (-) optical isomers have little effect on the fast current, yet produce a
marked reduction in the magnitude of the slow inward current. The different effects of the stereoisomers of verapamil and D-600 on these two depolarizing ionic currents provide circumstantial evidence that each isomer of these drugs may bind to different specific membrane sites to alter transmembrane sodium or calcium conductance. The purpose of the present study was to investigate the possible different electrophysiological effects of the racemic compounds and optical isomers of disopyramide and quinidine on canine cardiac Purkinje fibers.

Methods

Adult mongrel dogs of either sex, weighing 12-15 kg, were anesthetized with sodium pentobarbital (30 mg/kg, iv). Their hearts were removed rapidly through a right thoracotomy and immersed in cool oxygenated Tyrode's solution. Free-running Purkinje fiber bundles were excised from the right and left ventricles. The preparations were pinned to the floor of a Lucite muscle chamber (7-ml volume) and superfused continuously (7 ml/min) with Tyrode's solution gassed with 95% O₂-5% CO₂. The composition of the Tyrode's solution (mM) was Na⁺, 138; K⁺, 4.0; Ca²⁺, 1.25; HCO₃⁻, 20.0; H₂PO₄⁻, 0.9; Mg²⁺, 0.5; and glucose, 5.5. The osmolarity of the solution was 285 mOsm/liter, and the pH was 7.40 ± 0.05. Throughout each experiment, temperature was maintained at 37 ± 0.2°C by heating the muscle chamber with a circulating water bath. Temperature was monitored with a thermistor probe (Yellow Springs Instruments Co.) which was placed in the Tyrode's solution 2-3 mm from the preparation.

The preparations were stimulated at a constant basic cycle length of 800 msec with a custom-designed precision digital stimulator and waveform generator (Bloom Associates, Ltd.) via a bipolar extracellular (Teflon-coated) stainless steel electrode bared at the tip. Constant current extracellular stimuli were 1 msec in duration and 1.5-2.0 times diastolic threshold measured in the control state. Characteristics of the extracellular stimulus were not changed thereafter.

Conventional microelectrode techniques were used to record transmembrane action potentials (Draper and Weidmann, 1951). The glass microelectrodes were filled with 3 M KCl and their tip resistances ranged from 5-15 MΩ. The reference electrode was a second KCl-filled microelectrode, the tip of which was located very near the site of impalement by the recording microelectrode. Following completion of each experiment, the microelectrode used to record intracellular potentials was withdrawn to the extracellular space, and the zero potentials recorded from each electrode were observed.

Throughout each experiment, the following action potential characteristics were monitored: the membrane activation voltage measured at the onset of phase 0, action potential amplitude (measured from the onset of phase 0 to the peak of the overshoot), action potential duration at 50% and 90% repolarization (based on 50% and 90% of the action potential amplitude), and the maximum dV/dt of phase 0. Conduction time was measured from the onset of the transmembrane action potential to the peak deflection of a bipolar electrogram recorded from the distal portion of the Purkinje fiber. We also measured the minimum charge required to meet the liminal length requirements for all-or-none depolarization (Fozzard and Schoenberg, 1972). Constant current pulses 10 msec in duration were delivered intracellulary 800 msec following the last action potential of a train of 10 action potentials elicited by extracellular stimulation, using rapidly switching relays for intracellular stimulation and recording through a single microelectrode (Moore and Bloom, 1969). The minimum current required to elicit all-or-none depolarization in long (>10 mm) canine cardiac Purkinje fibers at a pulse duration of 10 msec is within 5% of the minimum current at a pulse duration of 100 msec, for practical purposes, rheobase (unpublished observations of Victor Elharrar and Milton Pressler). These data are expressed as the minimum current required to elicit all-or-none depolarization. Data were displayed on a Tektronix 5100 series oscilloscope and permanently stored on Polaroid film.

Two series of experiments were performed to determine the effects of the optical isomers of disopyramide and quinidine on the electrophysiological properties of isolated Purkinje fibers. Initially, the time course of the effects of these antiarrhythmic drugs was studied. Following a control period of 30 minutes, the preparation was superfused with the antiarrhythmic drug at a concentration of 1 X 10⁻⁵ M for 60 minutes. Impalement of the same cell was maintained for the duration of each study.

In a second series of experiments, concentration-response studies were performed with the antiarrhythmic agents at concentrations of 1 X 10⁻⁵ M, 3 X 10⁻⁶ M, and 1 X 10⁻⁵ M. Each concentration of drug was studied in a separate set of experiments (noncumulative concentration studies) and the various electrophysiological parameters were monitored continuously. The Purkinje fiber preparations were exposed to each concentration of drug for 60 minutes, after which the various action potential parameters, conduction time, and excitability were determined. The 60-minute time point was selected because drug effects appeared to reach steady state at approximately 30 minutes of drug exposure (see time-course studies). The drug concentrations selected for study were roughly comparable to a range of concentrations considered to be therapeutic (Winkle et al., 1975). Precise extrapolation of a selected drug concentration in this study to a specific antiarrhythmic drug level in patients is difficult because of variability in protein binding and effective drug levels. However, the range of concentra-
ELECTROPHYSIOLOGY OF DISOPYRAMIDE AND QUINIDINE/Mirro et al. 869

The effects of disopyramide (1 × 10^{-5} M) in three typical experiments are depicted in Figure 1. Racemic disopyramide prolonged action potential duration by 20 msec after 15 minutes of drug exposure (Fig. 1, panels C and D). Similarly, (+)-disopyramide (1 × 10^{-5} M) superfused for 15 minutes prolonged Purkinje fiber action potential duration by 20 msec (Fig. 1, A and B). In contrast, the (-) optical isomer of disopyramide (1 × 10^{-5} M) produced shortening of action potential duration by 20 msec when measured at 90% repolarization (Fig. 1, E and F). Thus, (+) and racemic disopyramide prolonged repolarization, whereas (-) disopyramide exerted a directionally opposite effect and hastened repolarization.

The time course of the effects of (+)-, racemic, and (-)-disopyramide (1 × 10^{-5} M) on Purkinje fiber action potential duration is shown in Figure 2.

Both (+) and racemic disopyramide significantly prolonged action potential duration after 5 minutes of drug exposure. This effect increased throughout 60 minutes of drug exposure, although the major effect occurred within the first 30 minutes. Conversely, (-)-disopyramide shortened action potential duration following 5 minutes of drug exposure. Superfusion with the (-) optical isomer for 60 minutes produced gradual shortening of the Purkinje fiber action potential duration, although most shortening occurred within the first 30 minutes. Thus, the effects of the (+) isomer on action potential duration predominated over the effects of the (-) isomer, since the racemic compound prolonged action potential duration. The effects of (+)-, racemic, and (-)-disopyramide on action potential duration were partially, but not completely, reversed after 60 minutes of washout (data not shown).

In another series of experiments, Purkinje fibers were exposed to a mixture of (+)-disopyramide (5 × 10^{-6} M) and (-)-disopyramide (5 × 10^{-6} M) for 60 minutes. This combination of stereoisomers, equivalent to clinically available racemic disopyramide, prolonged action potential duration by 10% (data not shown), a change similar to the prolongation seen when the commercially available racemic disopyramide was administered (Fig. 2).

As shown in Table 1, in contrast to the stereospecific effects of disopyramide on action potential duration at 50% and 90% of repolarization, (+)-, racemic, and (-)-disopyramide (1 × 10^{-5} M) exerted directionally similar effects on dV/dt of phase 0, conduction time, and current requirements for all-or-none depolarization throughout 60 minutes of exposure to drug, although the decrease in dV/dt...
Table 1  Time Course of the Effects of Racemic Disopyramide and Its Optical Isomers on Canine Cardiac Purkinje Fibers

<table>
<thead>
<tr>
<th></th>
<th>Control (n)</th>
<th>15 min</th>
<th>30 min</th>
<th>45 min</th>
<th>60 min</th>
</tr>
</thead>
<tbody>
<tr>
<td>APA (nsec)</td>
<td>(+) 128 ± 4</td>
<td>128 ± 4</td>
<td>127 ± 4</td>
<td>126 ± 4</td>
<td>127 ± 3</td>
</tr>
<tr>
<td></td>
<td>(-) 123 ± 3</td>
<td>120 ± 6</td>
<td>122 ± 3</td>
<td>121 ± 5</td>
<td>119 ± 5</td>
</tr>
<tr>
<td>MAV (nsec)</td>
<td>(+) 95 ± 3</td>
<td>94 ± 3</td>
<td>92 ± 3</td>
<td>92 ± 4</td>
<td>93 ± 4</td>
</tr>
<tr>
<td></td>
<td>(-) 90 ± 5</td>
<td>89 ± 4</td>
<td>89 ± 3</td>
<td>90 ± 2</td>
<td>89 ± 7</td>
</tr>
<tr>
<td>dV/dt (V/sec)</td>
<td>(+) 683 ± 111</td>
<td>623 ± 102*</td>
<td>543 ± 108*</td>
<td>563 ± 94*</td>
<td>547 ± 109*</td>
</tr>
<tr>
<td></td>
<td>(-) 603 ± 84</td>
<td>493 ± 87*</td>
<td>507 ± 84*</td>
<td>497 ± 112*</td>
<td>480 ± 105*</td>
</tr>
<tr>
<td>Ia (n AMP)</td>
<td>(+) 410 ± 142</td>
<td>440 ± 166</td>
<td>490 ± 170</td>
<td>493 ± 162*</td>
<td>507 ± 164*</td>
</tr>
<tr>
<td></td>
<td>(-) 245 ± 148</td>
<td>290 ± 177</td>
<td>300 ± 167*</td>
<td>305 ± 156*</td>
<td>320 ± 151*</td>
</tr>
<tr>
<td>CT (msec)</td>
<td>(+) 3.3 ± 1.2</td>
<td>3.4 ± 1.5*</td>
<td>3.5 ± 1.1*</td>
<td>3.7 ± 1.1*</td>
<td>3.6 ± 1.2*</td>
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<tr>
<td></td>
<td>(-) 4.1 ± 1.2</td>
<td>4.2 ± 1.1*</td>
<td>4.2 ± 1.2*</td>
<td>4.3 ± 1.3*</td>
<td>4.2 ± 1.2*</td>
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<td>APD50 (msec)</td>
<td>(+) 309 ± 50</td>
<td>328 ± 46*</td>
<td>341 ± 42*</td>
<td>334 ± 44*</td>
<td>337 ± 45*</td>
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<td></td>
<td>(-) 302 ± 43</td>
<td>320 ± 43*</td>
<td>311 ± 31*</td>
<td>305 ± 33*</td>
<td>309 ± 27*</td>
</tr>
<tr>
<td>APD90 (msec)</td>
<td>(+) 333 ± 49</td>
<td>240 ± 36</td>
<td>239 ± 34</td>
<td>244 ± 36</td>
<td>251 ± 32*</td>
</tr>
<tr>
<td></td>
<td>(-) 267 ± 26</td>
<td>250 ± 27</td>
<td>233 ± 26*</td>
<td>228 ± 31*</td>
<td>223 ± 30*</td>
</tr>
</tbody>
</table>

Values = mean ± SD; n = number of Purkinje fiber experiments. (+) and (-) = positive and negative optical isomer, respectively; R = racemic compound; APA = action potential amplitude in millivolts; MAV = membrane activation voltage in millivolts; dV/dt = maximum rate of rise of phase 0 in volts per second; Ia = intracellular constant current stimulus threshold requirement for all-or-none depolarization in nano-amperes; CT = conduction time in milliseconds; APD50 = action potential duration measured at 50% repolarization in milliseconds. APD90 = action potential duration measured at 50% repolarization in milliseconds.

* P < 0.05 compared to control.

Table 2  Concentration-Dependent Effects of Racemic Disopyramide and Its Optical Isomers on Canine Cardiac Purkinje Fibers

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>1 x 10⁻³</th>
<th>Δ</th>
<th>Control</th>
<th>3 x 10⁻³</th>
<th>Δ</th>
<th>Control</th>
<th>1 x 10⁻²</th>
<th>Δ</th>
</tr>
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<tbody>
<tr>
<td>APA (mV)</td>
<td>(+) 124 ± 5</td>
<td>122 ± 5</td>
<td>-2</td>
<td>125 ± 6</td>
<td>-3</td>
<td>128 ± 4</td>
<td>127 ± 3</td>
<td>-1</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(-) 128 ± 3</td>
<td>126 ± 3</td>
<td>-2</td>
<td>125 ± 5</td>
<td>-3</td>
<td>123 ± 3</td>
<td>119 ± 5</td>
<td>-4</td>
<td></td>
</tr>
<tr>
<td>MAV (mV)</td>
<td>(+) 90 ± 4</td>
<td>88 ± 3</td>
<td>-2</td>
<td>91 ± 3</td>
<td>-3</td>
<td>95 ± 3</td>
<td>93 ± 4</td>
<td>-2</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(-) 94 ± 4</td>
<td>93 ± 4</td>
<td>-1</td>
<td>92 ± 3</td>
<td>-1</td>
<td>95 ± 2</td>
<td>91 ± 2</td>
<td>-4</td>
<td></td>
</tr>
<tr>
<td>dV/dt (V/sec)</td>
<td>(+) 519 ± 74</td>
<td>440 ± 75</td>
<td>-79</td>
<td>588 ± 135</td>
<td>-136</td>
<td>683 ± 111</td>
<td>547 ± 109*</td>
<td>-136</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(-) 612 ± 124</td>
<td>564 ± 128</td>
<td>-48</td>
<td>532 ± 41</td>
<td>-84</td>
<td>647 ± 109</td>
<td>543 ± 125*</td>
<td>-144</td>
<td></td>
</tr>
<tr>
<td>Ia (n AMP)</td>
<td>(+) 278 ± 104</td>
<td>316 ± 137</td>
<td>+38</td>
<td>264 ± 102</td>
<td>+94</td>
<td>410 ± 142</td>
<td>507 ± 164*</td>
<td>+97</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(-) 282 ± 125</td>
<td>232 ± 21</td>
<td>+56</td>
<td>322 ± 17</td>
<td>0</td>
<td>368 ± 12</td>
<td>42 ± 1.2*</td>
<td>+0.4</td>
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</tr>
<tr>
<td>CT (msec)</td>
<td>(+) 2.4 ± 0.9</td>
<td>2.8 ± 0.9</td>
<td>+0.2</td>
<td>2.9 ± 0.9</td>
<td>+0.1</td>
<td>3.1 ± 1.2</td>
<td>3.6 ± 1.2*</td>
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<tr>
<td></td>
<td>(-) 3.6 ± 0.8</td>
<td>3.1 ± 0.4</td>
<td>+0.2</td>
<td>3.2 ± 0.7</td>
<td>-2</td>
<td>3.8 ± 1.2</td>
<td>4.2 ± 1.2*</td>
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<tr>
<td>APD50 (msec)</td>
<td>(+) 309 ± 23</td>
<td>321 ± 23</td>
<td>+12</td>
<td>284 ± 45</td>
<td>-48</td>
<td>309 ± 50</td>
<td>337 ± 45**</td>
<td>+28</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(-) 257 ± 34</td>
<td>281 ± 25*</td>
<td>+28</td>
<td>311 ± 34</td>
<td>+31</td>
<td>302 ± 43</td>
<td>328 ± 47**</td>
<td>+26</td>
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<tr>
<td>APD90 (msec)</td>
<td>(+) 268 ± 19</td>
<td>269 ± 17</td>
<td>+1</td>
<td>276 ± 24</td>
<td>-12</td>
<td>334 ± 49</td>
<td>309 ± 27*</td>
<td>-25</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(-) 231 ± 29</td>
<td>237 ± 51</td>
<td>+6</td>
<td>217 ± 24</td>
<td>+24</td>
<td>233 ± 40</td>
<td>251 ± 32*</td>
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<tr>
<td></td>
<td>(+) 201 ± 28</td>
<td>217 ± 16</td>
<td>+16</td>
<td>237 ± 40</td>
<td>-12</td>
<td>231 ± 40</td>
<td>238 ± 43*</td>
<td>+7</td>
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<td></td>
<td>(-) 209 ± 13</td>
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<td>304 ± 35</td>
<td>-12</td>
<td>267 ± 26</td>
<td>223 ± 30</td>
<td>-44</td>
<td></td>
</tr>
</tbody>
</table>

Values = mean ± SD for 5-6 experiments at each drug concentration; Δ = difference between control and drug effect means; other abbreviations as in Table 1.

* P < 0.05 compared to control; ** P < 0.01 compared to control.

of phase 0 caused by (−)-disopyramide did not attain statistical significance. Action potential amplitude and membrane activation voltage were not altered consistently in these experiments. The concentration of 1 x 10⁻³ m disopyramide was selected for these studies since it is roughly comparable to the concentration of racemic disopyramide present in the plasma of patients during drug therapy (Winkle et al., 1975; Niarchos, 1976).

Concentration-response studies were also performed with (+)-, racemic, and (−)-disopyramide, as illustrated in Table 2. The prolongation of action
potential duration at 50% and 90% of repolarization observed with (+) and racemic disopyramide was concentration dependent. The shortening of action potential duration at 50% and 90% of repolarization observed with (−)-disopyramide was also concentration dependent. All three compounds studied exerted concentration-dependent effects on dV/dt of phase 0, conduction time, and current requirements for all-or-none depolarization. At the highest concentration (1 × 10⁻⁵ M), none of the three compounds reduced action potential amplitude or membrane activation voltage significantly.

**Effects of Quinidine and Quinine on the Electrophysiological Properties of Canine Cardiac Purkinje Fibers**

In a single experiment (Fig. 3, panels E and F), quinidine (1 × 10⁻⁵ M) prolonged action potential duration by 15 msec after 15 minutes of drug superfusion. In contrast, quinine (5 × 10⁻⁶ M) superfused over an isolated Purkinje fiber for 15 minutes shortened action potential duration by 30 msec (Fig. 3, A and B). Therefore, the optical isomers of this cinchona alkaloid produced directionally opposite effects on the terminal phase of repolarization. A mixture of quinine (5 × 10⁻⁶ M) and quinidine (5 × 10⁻⁶ M) prolonged action potential duration by only 5 msec. The time courses of the effects of quinidine and quinine on Purkinje fiber action potential duration are provided in Figure 4. Quinidine significantly prolonged action potential duration throughout 60 minutes of drug exposure. Conversely, quinine shortened action potential duration throughout 60 minutes of drug superfusion. In both instances, the major effects on action potential duration occurred by 30 minutes. Administration of a mixture of quinine (5 × 10⁻⁶ M) and quinidine (5 × 10⁻⁶ M) did not change action potential duration significantly throughout 60 minutes of drug exposure.

**Figure 3** Effects of quinine and quinidine on action potential duration of canine cardiac Purkinje fibers. A: Control for B; B: quinine (1 × 10⁻⁵ M) superfused for 15 minutes; C: control for D; D: quinidine (5 × 10⁻⁶ M) and quinine (5 × 10⁻⁶ M) superfused for 15 minutes; E: control for F; F: Quinidine (1 × 10⁻⁵ M) superfused for 15 minutes. Zero potential is indicated in each panel. Calibrations: horizontal bar = 50 msec; vertical bar = 15 mV.

**Figure 4** Time course of the effects of quinidine, quinine, and an equimolar mixture of quinidine/quinine on action potential duration of canine cardiac Purkinje fibers. Values are means ± SE for 5-6 experiments. *P < 0.05 compared to control.

Despite the stereospecific effects of quinidine and quinine on Purkinje fiber action potential duration measured at 90% of repolarization, as shown in Table 3 both compounds exerted similar effects on dV/dt of phase 0, conduction time, and current requirements for all-or-none depolarization. Neither drug significantly altered action potential amplitude or membrane activation voltage throughout 60 minutes of drug exposure. Quinidine shortened action potential duration measured at 50% repolarization, whereas quinidine did not affect this parameter. The effects observed with quinidine on action potential duration were not reversed completely within 60 minutes of washout; however its effects on all other parameters had returned to the control state (data not shown). Quinidine and quinine were studied at a concentration of 1 × 10⁻⁵ M, since this is roughly comparable to concentrations attainable clinically (Sokolow, 1950; Winkle et al., 1975).

Concentration-response studies also were performed with both quinidine and quinine. As shown in Table 4, quinidine produced a concentration-related increase in action potential duration. Quinidine produced a concentration-related shortening of action potential duration measured at 90% repolarization. Despite the directionally opposite effects of quinidine and quinine on the terminal phase of repolarization, neither compound affected significantly the plateau phase (APD₉₀) of the transmembrane action potentials recorded in these experiments.

Quinidine and quinine produced similar concentration-related effects on dV/dt of phase 0. Neither compound affected action potential amplitude or membrane activation voltage. Quinidine and quinine also exerted directionally similar effects on conduction time and current requirements for all-or-none depolarization. The combination of quinidine 5 × 10⁻⁶ M and quinine 5 × 10⁻⁶ M affected...
TABLE 3  
Time Course of Electrophysiological Effects of Quinidine, Quinine, and an Equimolar Mixture of Quinidine and Quinine on Canine Cardiac Purkinje Fibers

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>15 min</th>
<th>30 min</th>
<th>45 min</th>
<th>60 min</th>
</tr>
</thead>
<tbody>
<tr>
<td>APA (mV)</td>
<td>(+) 129 ± 2 (6)</td>
<td>130 ± 3</td>
<td>128 ± 5</td>
<td>126 ± 5</td>
<td>126 ± 6</td>
</tr>
<tr>
<td>MAV (mV)</td>
<td>(R) 130 ± 5 (5)</td>
<td>129 ± 4</td>
<td>130 ± 2</td>
<td>130 ± 3</td>
<td>130 ± 3</td>
</tr>
<tr>
<td>dV/dt (V/sec)</td>
<td>(+) 707 ± 145 (6)</td>
<td>600 ± 110**</td>
<td>587 ± 67</td>
<td>540 ± 96*</td>
<td>517 ± 100*</td>
</tr>
<tr>
<td>CT (msec)</td>
<td>(R) 690 ± 76 (5)</td>
<td>636 ± 95</td>
<td>608 ± 86</td>
<td>612 ± 72</td>
<td>604 ± 80</td>
</tr>
<tr>
<td>Ia (n AMP)</td>
<td>(R) 358 ± 155 (5)</td>
<td>392 ± 190</td>
<td>440 ± 152</td>
<td>444 ± 131</td>
<td>450 ± 161</td>
</tr>
<tr>
<td>APD90 (msec)</td>
<td>(R) 315 ± 18 (5)</td>
<td>318 ± 13</td>
<td>321 ± 14</td>
<td>320 ± 14</td>
<td>320 ± 16</td>
</tr>
<tr>
<td>APD90 (msec)</td>
<td>(R) 248 ± 23 (5)</td>
<td>248 ± 18</td>
<td>248 ± 22</td>
<td>248 ± 20</td>
<td>248 ± 22</td>
</tr>
</tbody>
</table>

| APA (mV) | (+) 128 ± 5 (6) | 125 ± 5 | 128 ± 3 | 126 ± 3 | 126 ± 6 |
| MAV (mV) | (R) 130 ± 5 (5) | 129 ± 4 | 130 ± 2 | 130 ± 3 | 130 ± 3 |
| dV/dt (V/sec) | (+) 707 ± 145 (6) | 600 ± 110** | 587 ± 67 | 540 ± 96* | 517 ± 100* |
| CT (msec) | (R) 690 ± 76 (5) | 636 ± 95 | 608 ± 86 | 612 ± 72 | 604 ± 80 |
| Ia (n AMP) | (R) 358 ± 155 (5) | 392 ± 190 | 440 ± 152 | 444 ± 131 | 450 ± 161 |
| APD90 (msec) | (R) 315 ± 18 (5) | 318 ± 13 | 321 ± 14 | 320 ± 14 | 320 ± 16 |
| APD90 (msec) | (R) 248 ± 23 (5) | 248 ± 18 | 248 ± 22 | 248 ± 20 | 248 ± 22 |

Abbreviations as in Tables 1 and 2.

* P < 0.05 compared to control; ** P < 0.01 compared to control.

TABLE 4  
Concentration-Dependent Effects of Quinidine, Quinine, and an Equimolar Mixture of Quinidine and Quinine on Canine Cardiac Purkinje Fibers

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>10−4</th>
<th>Δ</th>
<th>Control</th>
<th>10−4</th>
<th>Δ</th>
</tr>
</thead>
<tbody>
<tr>
<td>APA (mV)</td>
<td>(+) 128 ± 5 (6)</td>
<td>125 ± 5</td>
<td>-1</td>
<td>128 ± 3</td>
<td>126 ± 3</td>
<td>0</td>
</tr>
<tr>
<td>MAV (mV)</td>
<td>(R) 130 ± 5 (5)</td>
<td>129 ± 4</td>
<td>-2</td>
<td>128 ± 3</td>
<td>126 ± 3</td>
<td>-2</td>
</tr>
<tr>
<td>dV/dt (V/sec)</td>
<td>(+) 707 ± 145 (6)</td>
<td>600 ± 110**</td>
<td>-2</td>
<td>128 ± 3</td>
<td>126 ± 3</td>
<td>-2</td>
</tr>
<tr>
<td>CT (msec)</td>
<td>(R) 690 ± 76 (5)</td>
<td>636 ± 95</td>
<td>-44</td>
<td>652 ± 65</td>
<td>560 ± 72*</td>
<td>-92</td>
</tr>
<tr>
<td>Ia (n AMP)</td>
<td>(R) 358 ± 155 (5)</td>
<td>392 ± 190</td>
<td>0</td>
<td>440 ± 152</td>
<td>340 ± 104*</td>
<td>+10</td>
</tr>
<tr>
<td>APD90 (msec)</td>
<td>(R) 315 ± 18 (5)</td>
<td>318 ± 13</td>
<td>0</td>
<td>321 ± 14</td>
<td>320 ± 14</td>
<td>+10</td>
</tr>
<tr>
<td>APD90 (msec)</td>
<td>(R) 248 ± 23 (5)</td>
<td>248 ± 18</td>
<td>0</td>
<td>248 ± 22</td>
<td>248 ± 20</td>
<td>+10</td>
</tr>
</tbody>
</table>

Values = mean ± sd for 5-6 experiments at each drug concentration. Abbreviations as in Tables 1-3.

* P < 0.05 compared to control; ** P < 0.01 compared to control.

Discussion

This study demonstrates that the effects of disopyramide and quinidine on action potential duration of canine cardiac Purkinje fibers are influenced by the stereochemochemical properties of these compounds. Racemic disopyramide, (+)-disopyramide, and quinidine prolong action potential duration, whereas (−)-disopyramide and quinidine shorten action potential duration. A number of investigators has documented that racemic disopyramide (Kus and Sasyiniuk, 1975; Danilo et al., 1977) and quinidine (Weidmann, 1955; Hoffman, 1958) prolong the terminal phase of repolarization. It has been postulated that this effect represents one major mechanism whereby these two agents abolish re-entrant ventricular arrhythmias (McQuillan and Sasyiniuk, 1975). Our study confirms these earlier observations.
observations and further demonstrates that the effects of these two drugs on action potential duration depend importantly on which optical stereoisomer is being administered.

Previous reports have indicated that certain effects of antiarrhythmic drugs on electrophysiological properties of isolated cardiac tissue are stereoselective. For example, the negative optical isomer of propranolol appears to antagonize the effects of β-adrenergic receptor stimulation approximately 100 times more potently than the positive optical isomer (Barrett and Cullum, 1968), whereas racemic propranolol and both optical isomers exert identical direct membrane effects on isolated cardiac tissue (Cotart and Meldrum, 1971). Verapamil and D-600 also exert stereosepecific effects on membrane ionic conductance (Bayer et al., 1975; Ebara and Kaufman, 1978). In isolated cat papillary muscle, the positive optical isomers of verapamil and D-600 specifically inhibit the fast inward current. The negative optical isomers are approximately one order of magnitude more potent than the positive optical isomers in depressing the slow inward current. These data suggest that these compounds may interact stereospecifically with transmembrane ionic channels (Bayer et al., 1975; Reuter, 1979). However, both optical isomers of these compounds exert equal effects on the terminal phase of repolarization, suggesting nonstereoselective effects on outward currents. In the present study, the directional changes in action potential duration depend on which optical isomer was administered, suggesting that these antiarrhythmic compounds may bind stereoselectively to specific membrane sites and thus interact with ionic channels responsible for action potential duration. Conversely, all agents studied depressed dV/dt of phase 0 and conduction speed, suggesting that these latter electrophysiological effects were mediated nonstereospecifically. Voltage clamp experiments in frog atrium and squid axon have demonstrated that quinidine reduces transmembrane potassium conductance, which may explain the effects of this compound on repolarization (Ducouret, 1976; Yeh and Narahashi, 1976). A number of investigators have speculated that the effects of quinidine and disopyramide on action potential duration is due to a decrease in outward potassium currents (Armsdorf and Mehlman, 1978; Hauswirth and Singh, 1979). However, it is not possible, on the basis of our studies, to determine whether disopyramide and quinidine stereospecifically affect a single ionic current to alter repolarization or whether the optical isomers of these drugs produce differing effects on repolarization by altering different ionic mechanisms. Further studies, particularly current and voltage clamp experiments, might provide more quantitative data regarding the extent to which these drugs might stereospecifically alter active or passive membrane properties.

In our study, racemic disopyramide and its (+) optical isomer prolonged action potential duration, whereas the (−) isomer hastened repolarization. One might speculate that the (+) isomer associates with higher affinity with a membrane site that ultimately causes repolarization delay. This effect would surpass the effects of the lower affinity association of the (−) isomer with an alternate membrane site. A true cancellation of effects on repolarization was noted with the mixture of quinidine and quinine, so one would reason that this effect was due to similar affinities of these compounds for association with their respective membrane sites. Such reasoning is, of course, purely speculative, since antiarrhythmic compounds may alter repolarization speed by a number of mechanisms, including alteration of both active and passive membrane properties.

Recently we have reported the stereoselective interactions of (+)- and (−)-disopyramide with muscarinic cholinergic receptors in atrium and cardiac ventricular muscle fibers (Mirro et al., 1979a). In that study, the (+) isomer was approximately three times more potent than the (−) isomer at antagonizing the electrophysiological effects of cholinergic stimulation of isolated guinea pig right atria. These observations were substantiated by direct receptor-binding studies in which the (+) isomer of disopyramide was approximately three times more potent than the (−) isomer in competing with 3H-quinuclidinyl benzilate (QNB) for binding to atrial muscarinic receptors. In that same study, quinidine and quinine were equipotent in antagonizing the effects of cholinergic stimulation and competing with 3H-QNB for binding to muscarinic receptors. Therefore, the stereochemistry of disopyramide appears to influence importantly both a direct effect (repolarization) and an indirect effect (anticholinergic) of this compound. The optical stereochermistry of quinidine, however, appears to influence directly effects (repolarization) but not indirect effects (anticholinergic). The effects of disopyramide and quinidine on repolarization are probably not due to occupation of muscarinic receptors by these drugs, since previous work has documented that atropine does not alter repolarization at concentrations which result in complete muscarinic receptor blockade (Mirro et al., 1980b).

Quinidine and quinine have long been recognized to possess differing potencies as antiarrhythmic agents (Frey, 1918; Alexander et al., 1947). However, in vivo studies have failed to demonstrate differing effects on experimental atrial and ventricular arrhythmias (Klevans et al., 1977). Obvious differences between experimental arrhythmias and clinically observed rhythm disturbances could possibly explain these discrepancies. It is possible, however, that the differing effects of quinidine and quinine observed in the present in vitro studies might explain the differing clinical efficacy of these optical isomers.

The diametrically opposed effects of the optical isomers of disopyramide and quinidine on action
potential duration and their similar effects on current requirements, dV/dt of phase 0, and conduction may provide a useful tool to allow association of antiarrhythmic effectiveness with particular electrophysiological effects. Class I antiarrhythmic drugs such as quinidine and disopyramide typically decrease excitability, reduce dV/dt of phase 0, and prolong action potential duration and refractory period (Rosen and Hoffman, 1973; Hauswirth and Singh, 1979). However, it has yet to be determined which, if any, of these electrophysiological parameters most importantly determines antiarrhythmic drug effect. The results of our study indicate that one might determine, for example, which effect of disopyramide, reduced dV/dt of phase 0, or prolonged refractoriness, was the more important by administering the optical isomers of this drug in carefully designed animal or clinical studies of antiarrhythmic efficacy. Commercially available disopyramide is constituted of equal mixtures of the two optical isomers. If one optical isomer of disopyramide is more antiarrhythmic in clinical studies than the other isomer, administration of only that optical isomer might, because of a significantly lower dose requirement, reduce the incidence of adverse dose-related side effects or toxicity.

Acknowledgments

We gratefully acknowledge the excellent technical assistance of David Mendel and Darlene Massad, the editorial assistance of Karen Kinney, and the secretarial assistance of Marsha Meece and Shelia Cauley.

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M J Mirro, A M Watanabe and J C Bailey

Circ Res. 1981;48:867-874
doi: 10.1161/01.RES.48.6.867

Circulation Research is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7330. Online ISSN: 1524-4571

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