Adverse Hemodynamic Effects of Intravenous Disopyramide Compared with Quinidine in Conscious Dogs

RICHARD A. WALSH, M.D., AND LAWRENCE D. HORWITZ, M.D.

SUMMARY Disopyramide resembles quinidine electrophysiologically, but its effect on left ventricular function has not been clarified. Twelve awake dogs were instrumented for measurement of cardiac output, left ventricular pressure and its maximal first derivative (dP/dt max), and left atrial and aortic pressures. Disopyramide or quinidine at identical, clinically relevant doses (1 and 5 mg/kg i.v.) was infused over 5 minutes at each level. Peak changes after disopyramide 1 mg/kg included increases in heart rate (34%), mean aortic pressure (24%) and systemic vascular resistance (33%), and decreases in stroke volume (16%) and dP/dt max (19%). With disopyramide at 5 mg/kg these changes were of greater magnitude (e.g., dP/dt – 36%). Quinidine at both doses caused no changes except a 13% decrease in vascular resistance at 5 mg/kg. Heart rate with disopyramide increased after propranolol (1 mg/kg i.v.), was unchanged after atropine (0.1 mg/kg i.v.), and slowed after propranolol and atropine. Phenoxybenzamine (2 mg/kg i.v.) did not prevent the rise in systemic vascular resistance produced by disopyramide. Thus, disopyramide in clinical dosages exerts opposing direct and indirect effects on cardiac pacemakers and, unlike quinidine, is a potent myocardial depressant and vasoconstrictor in the conscious dog.

DISOPYRAMIDE is a recently released antiarrhythmic agent whose direct electrophysiologic properties resemble those of quinidine. Disopyramide reduces the rate of phase-4 depolarization, diminishes myocardial conduction velocity and prolongs the effective and functional refractory periods in the atria, atroventricular (AV) node and ventricles. However, autonomically mediated reflex effects, such as quinidine’s vagolytic effect on the AV node and the blockade of peripheral vascular α receptors, have not been shown with disopyramide. Although the efficacy of disopyramide for prevention of certain arrhythmias is well established, little is known about its hemodynamic effects, and there is reason for concern that disopyramide could induce potentially detrimental changes in myocardial function. In a study of an acute, open-chest animal preparation, Mathur found evidence of a dose-related depression in myocardial contractile force. Parenteral disopyramide administration to patients with cardiac dysfunction has reduced cardiac output and increased peripheral vascular resistance. In addition, there have been occasional cases in which administration of this agent to patients with cardiac disease may have provoked the onset of congestive heart failure.

There have been no studies of the effects of disopyramide on left ventricular function in conscious animal models, and data in man have been limited. It is not known whether this agent can induce myocardial depression of sufficient magnitude to seriously impair cardiac function in clinical settings or cause potentially deleterious reflex cardiac or peripheral vascular effects.

We evaluated cardiac chronotropic and inotropic responses and changes in systemic vascular resistance due to disopyramide given intravenously in clinically relevant doses in normal, conscious dogs. The extent to which changes were modulated by the autonomic nervous system was assessed with pharmacologic agents that selectively block autonomic reflex effects on the cardiovascular system. Finally, direct and reflex effects observed with disopyramide and with identical doses of intravenous quinidine gluconate were compared.

Methods

Sterile thoracotomies were performed in 12 adult mongrel dogs that weighed 15–20 kg and were anesthetized with sodium pentobarbital (30 mg/kg i.v.). A precalibrated, solid-state pressure transducer (model P-18, Konigsberg Instruments Inc., Pasadena, California) was inserted into the left ventricle through a stab wound near the apex. In six dogs, an electromagnetic cuff-type flow probe (Zepeda Instruments, Seattle, Washington) was affixed to the ascending aorta. In five dogs, piezoelectric crystals were implanted across the greatest internal transverse diameter of the left ventricle, one on the anterior and the other on the posterior endocardial wall for the measurement of left ventricular internal diameter. Polyvinyl catheters were implanted in the left atrium and descending aorta of all dogs. Recording leads and catheters were exteriorized at the back of the neck. Each dog was allowed a minimum of 2 weeks for recovery from surgery before experiments began.

The solid-state pressure transducers were calibrated with a mercury manometer before implantation. These transducers have a natural frequency greater than 3000 Hz and do not change in sensitivity during implantation. At the beginning of each experiment, day-to-day zero drift was corrected by setting left ven-
tricular end-diastolic pressure equal to the mean left atrial pressure measured simultaneously by means of the implanted catheter. Statham P23Db external manometers were used to measure both left atrial and aortic pressures.

Aortic phasic flow was recorded with a Zepeda EDP2 square-wave flow meter. Flow probes were calibrated in vitro before implantation. Flow was assumed to be zero at end-diastole. Stroke volume was obtained by integration of the systolic portion of the phasic flow signal with an active resistance-capacitance network. Systemic resistance was calculated as (mean arterial pressure (mm Hg)/cardiac output (l/min) × 80 (dyn-sec-cm⁻¹). Left ventricular internal diameter was obtained with a sonocardiometer that measured the transit time of 5-MHz ultrasound between the two piezoelectric crystal transducers at a rate of 5000 samples/sec. The resolution of the instrument is approximately 0.07 mm. Left ventricular pressure was differentiated by an active resistance-capacitance network; signal amplitude decreased by 3 dB at 100 Hz. All signals were recorded on a Beckman RM oscillograph and an Ampex FR 1300A magnetic tape recorder.

During experiments, the dogs were unseeded and resting prone in a sling. Infusions of parenteral disopyramide (G.D. Searle and Company, Chicago, Illinois) were administered through the left atrial catheter over 5 minutes at the 1- and 5-mg/kg levels on different days. On another day, this protocol was repeated 15 minutes after administration of propranolol, 1 mg/kg iv. On a subsequent day, this protocol was modified by additional pretreatment using 0.1 mg/kg of atropine to observe the effects of disopyramide after β-adrenergic and parasympathetic blockade. Five dogs were also studied after pretreatment with phenoxybenzamine (2 mg/kg i.v.). Finally, to assess whether directional effects on dP/dt might be due to alterations in heart rate or afterload, we matched disopyramide-induced changes in heart rate and mean aortic pressure with phenylephrine and pacing in the same dog on different days. At least 48 hours for recovery and drug excretion was allowed between the drug protocols. The administered dosage of propranolol used abolished the effects of isoproterenol (3-5 μg/min i.v.) on heart rate and dP/dt max for 45 minutes beginning 15 minutes after propranolol was given. The administered dosage of atropine used abolished the effect on heart rate of acetylcholine (1.0 mg i.v.) on repeated challenge for 45 minutes beginning 10 minutes after atropine was given. The dosage of phenoxybenzamine blocked the pressor effect of phenylephrine infused at 0.07 mg/min for 10 minutes beginning 5 minutes after phenoxybenzamine. Finally, quinidine gluconate was administered on different days at 1- and 5-mg/kg infusions (0.6 mg/kg and 3 mg/kg, respectively, of quinidine base) over 5 minutes via the left atrial catheter, and peak effects were measured.

Statistical analyses were done by paired t tests, with each dog as its own control.

### Results

#### Effects of Disopyramide with Intact Autonomic Control (table 1)

Figure 1 shows a selected portion of an oscillograph record during an experiment with disopyramide. After a dose of 1 mg/kg given as an intravenous infusion over 5 minutes, there were increases in heart rate and

<table>
<thead>
<tr>
<th>Heart rate (beats/min)</th>
<th>Stroke volume (ml)</th>
<th>Cardiac output (l/min)</th>
<th>SVR (mm Hg)</th>
<th>MAP (mm Hg)</th>
<th>LAP (mm Hg)</th>
<th>dP/dt (mm Hg/sec)</th>
<th>LViD₅₄ (mm)</th>
<th>LViD₆₄ (mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control (mean ± sd)</td>
<td>79 ± 17</td>
<td>30 ± 5</td>
<td>2.52 ± 0.32</td>
<td>2674 ± 0.32</td>
<td>88 ± 6</td>
<td>4 ± 1</td>
<td>2678 ± 420</td>
<td>—</td>
</tr>
<tr>
<td>Change from control</td>
<td>124 ± 26</td>
<td>15 ± 3</td>
<td>10.07 ± 0.3</td>
<td>879 ± 558</td>
<td>21 ± 9</td>
<td>0.17 ± 3</td>
<td>477 ± 188</td>
<td>—</td>
</tr>
<tr>
<td>n</td>
<td>9</td>
<td>6</td>
<td>6</td>
<td>9</td>
<td>9</td>
<td>9</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>p</td>
<td>0.05</td>
<td>0.02</td>
<td>NS</td>
<td>0.02</td>
<td>NS</td>
<td>0.001</td>
<td>NS</td>
<td>—</td>
</tr>
</tbody>
</table>

1-mg/kg disopyramide infusion

| Control (mean ± sd)   | 89 ± 20           | —                      | —           | 97 ± 7      | 5 ± 3       | 3040 ± 588       | 43 ± 4      | 28 ± 3.4    |
| Change from control   | 152 ± 25          | —                      | —           | 134 ± 17    | 16 ± 4     | 1019 ± 602      | 44 ± 3      | 18 ± 2      |
| n                     | 5                 | —                      | —           | 5           | 5          | 5                 | 5           | 5           |
| p                     | 0.02              | —                      | —           | 0.02        | NS         | 0.05             | NS          | 0.001       |

5-mg/kg disopyramide infusion

Abbreviations: SVR = systemic vascular resistance; MAP = mean aortic pressure; LAP = mean left atrial pressure; LViD₅₄ and LViD₆₄ = the left ventricular internal transverse dimensions in diastole and systole, respectively, using ultrasonic crystals; Change from control = the mean differences from control 1 minute after disopyramide infusion; ↑ = increase; ↓ = decrease; dP/dt = first derivative of left ventricular pressure.
Left ventricular dP/dt max fell by 18% ($p < 0.001$) and 34% ($p < 0.05$) 1 minute after 1 and 5 mg/kg disopyramide. To assess whether directional effects on dP/dt might be due to increases in heart rate or afterload, we matched disopyramide-induced changes in heart rate and mean aortic pressure with phenylephrine and pacing in the same dog on different days. The results indicate that the increase in heart rate or mean aortic pressure has no effect on dP/dt (table 2). Left ventricular internal transverse diameter was measured in five dogs given 5-mg/kg infusions of disopyramide. End-diastolic diameter did not change despite the increase in heart rate. However, there was a significant ($p < 0.001$) increase (7.6 mm) in end-systolic diameter. This represents a 16% reduction in percent minor diameter shortening.

Effects of Autonomic Blocking Agents

Maximal heart rate responses to disopyramide without blocking agents and after propranolol or propranolol plus atropine are shown in figure 3. The
same dogs were not studied in all states. After propranolol alone, significant increases in heart rate occurred at both doses of disopyramide. After atropine and propranolol, the resting heart rate was initially high at 208 beats/min, but decreased with 1 mg/kg disopyramide to 180 beats/min ($p < 0.01$).

Peak increases in mean aortic pressure in response to 1 mg/kg with and without pretreatment with phenytoin (2 mg/kg) are shown in figure 4. The increase with disopyramide alone was 21 mm Hg (22%) ($p < 0.001$) in six dogs. Phenytoin given to five of these dogs did not prevent a 22-mm Hg peak increase (27%) after disopyramide.

**Discussion**

Given intravenously in doses used clinically for suppression of ventricular arrhythmias, disopyramide is a potent myocardial depressant in the conscious dog. The evidence for impairment of myocardial contractile function with disopyramide includes reductions of 18% and 34% in dP/dt max for dosages of 1 and 5 mg/kg, respectively, and diminished left ventricular ejection fractions, as estimated from diameter measurements. The alterations occurred in the presence of tachycardia and in the absence of changes in preload. The increase in afterload that occurred with disopyramide administration does not account for the changes in the rate of force development. We have shown that dP/dt max does not decrease with equivalent changes in aortic pressure and heart rate induced by phenylephrine and pacing (table 2). Afterload changes in this range do not consistently alter dP/dt max and influence extent of shortening only minimally in conscious dogs. Thus, the changes in the rate of force development and extent of shortening probably reflect substantial reductions in myocardial contractile force rather than responses to simultaneous changes in preload, afterload or heart rate.

The positive chronotropic effect of intravenous disopyramide has not been noted in previous animal investigations. This may relate to the use of open-

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**Table 2. Effect of Afterload on Disopyramide-induced Changes in dP/dt**

<table>
<thead>
<tr>
<th></th>
<th>Heart rate (beats/min)</th>
<th>Stroke volume (ml)</th>
<th>Cardiac output (l/min)</th>
<th>SVR (dyn-sec-cm⁻²)</th>
<th>MAP (mm Hg)</th>
<th>LAP (mm Hg)</th>
<th>dP/dt max (mm Hg/sec)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>96</td>
<td>25</td>
<td>2.41</td>
<td>3213</td>
<td>98</td>
<td>3</td>
<td>2403</td>
</tr>
<tr>
<td>Disopyramide (5 mg/kg)</td>
<td>138</td>
<td>16</td>
<td>2.25</td>
<td>4622</td>
<td>130</td>
<td>7</td>
<td>1602</td>
</tr>
<tr>
<td>Control</td>
<td>102</td>
<td>22</td>
<td>2.33</td>
<td>3326</td>
<td>93</td>
<td>4</td>
<td>2670</td>
</tr>
<tr>
<td>Phenylephrine and pacing</td>
<td>135</td>
<td>19</td>
<td>2.62</td>
<td>3966</td>
<td>130</td>
<td>6</td>
<td>2670</td>
</tr>
</tbody>
</table>

Disopyramide-induced changes in heart rate and mean arterial pressure were matched in the same animal on a different day using phenylephrine and pacing. Pacing and phenylephrine had no effect on dP/dt max.

Abbreviations: SVR = systemic vascular resistance; MAP = mean aortic pressures; LAP = mean left atrial pressure; dP/dt max = maximal first derivative of left ventricular pressure.
chest anesthetized preparations, which are often associated with high heart rates. In a human study using 1 mg/kg of intravenous disopyramide in healthy volunteers, a 20% increase in heart rate occurred. We noted 30% and 58% increases in heart rate at disopyramide levels of 1 and 5 mg/kg in conscious dogs. This is particularly striking in view of the concomitant increase in mean arterial pressure, which would be expected to lower heart rate through baroreceptor stimulation. Because the increment in heart rate was not prevented by prior β-adrenergic blockade, vagal withdrawal rather than sympathetic enhancement is probably the mechanism responsible for the tachycardia. This is not surprising, because anticholinergic side effects have been noted with oral administration of this agent. In our experiments with pharmacologic cardiac denervation, disopyramide caused a slowing in heart rate, which may result from a direct effect of disopyramide on the sinoatrial node, perhaps by reducing phase IV diastolic depolarization.

Disopyramide consistently increased mean arterial pressure and systemic vascular resistance. The α-blocking agent phenoxybenzamine failed to prevent or attenuate this pressor response. Therefore, α-adrenergic stimulation is not a factor in the drug-induced hypertension. Disopyramide may directly stimulate vascular smooth muscle or sensitize it to the effects of endogenous vasoactive substances.

Quinidine gluconate, a standard antiarrhythmic agent, was given in identical dosages for comparison with disopyramide. Blood levels of quinidine were below therapeutic values at the lower dosage, but were clearly in the therapeutic range with the higher dosage. No decrease in dP/dt max occurred in any dog with either dose of quinidine. The only significant hemodynamic change with quinidine was a decrease in systemic resistance at the higher dosage. The diminished resistance may be due to quinidine’s ability to block α receptors.

Although quinidine and disopyramide are electrophysiologically similar, their hemodynamic effects differ profoundly. We observed several hemodynamic alterations with disopyramide in our animal model that could have important deleterious effects if they occurred in clinical settings. The depression in left ventricular performance may be clinically important during acute drug administration in patients with myocardial dysfunction by inducing or worsening congestive heart failure. During acute myocardial infarction, disopyramide-induced increases in heart rate and mean arterial pressure could be associated with increased myocardial oxygen demand, which would be expected to exacerbate tissue hypoxia.

**Acknowledgments**

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**References**

Interventricular Septal Thickness and Left Ventricular Hypertrophy
An Echocardiographic Study

SANTOSH KANSAL, M.D., DAVID ROITMAN, M.D., AND L. THOMAS SHEFFIELD, M.D.

SUMMARY Septal and left ventricular posterior wall (LVPW) thicknesses and their ratios were studied at the left ventricular outflow tract and left ventricular cavity in 66 patients with echocardiographically diagnosed left ventricular concentric hypertrophy, 20 with idiopathic hypertrophic subaortic stenosis (IHSS), and 34 normal subjects. Concentric hypertrophy was due to hypertension in 41 subjects and to valvular disease in 15 subjects. Septal thickness in normal subjects was related to body surface area (p < 0.02). In 12% of normal subjects, 39% of patients with concentric hypertrophy and 95% with IHSS, the septal/LVPW ratio was ≥ 1.3. Thirty-two percent of patients with hypertension, 78% with aortic stenosis, and 60% with aortic insufficiency had septal/LVPW ratios ≥ 1.3 at left ventricular midcavity level.

In conclusion, a septal/LVPW thickness ratio of ≥ 1.3 is common in patients with concentric left ventricular hypertrophy and may also occur in normal subjects. A ratio ≥ 1.5 may be more specific for genetically determined asymmetric septal hypertrophy.

SINCE THE INTRODUCTION of the term asymmetric septal hypertrophy (ASH) in 1973, controversy has arisen regarding its clinical and echocardiographic significance. The diagnosis of ASH is based on echocardiographic analysis that shows disproportionate septal thickness and a ratio of septal-to-left ventricular free wall of 1.3 or more.

This specific ratio has led to study of the septum and its relation to the left ventricular free wall in many congenital and acquired cardiac diseases, and has revealed that many diseases, such as pulmonary hypertension,4 pulmonary stenosis,4 congenital malformation of the mitral valve,5,6 coarctation of the aorta, and aortic valvar disease6,7 manifest disproportionate septal thickness.

In this study we assessed the interventricular septal and left ventricular free wall thicknesses and their ratio in patients with concentric hypertrophy. We also compared patients who had idiopathic hypertrophic subaortic stenosis (IHSS) with normal subjects.

Subjects and Methods

One hundred twenty patients were studied, including 66 patients with concentric left ventricular hypertrophy, 20 patients with IHSS, and 34 normal subjects.

In the first group, the diagnosis of concentric hypertrophy was based on echocardiographic measurement of left ventricular posterior wall and interventricular septum thickness of ≥ 11 mm in the absence of a small left ventricular outflow tract or abnormal systolic anterior motion of the mitral valve. This hypertrophy was due to various primary conditions (table 1). In several patients more than one disease was present,
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