Electrophysiological Effects of Disopyramide in Patients with Bundle Branch Block

JAWAHAR M. DESAI, M.D., MELVIN SCHEINMAN, M.D., ROBERT W. PETERS, M.D., AND JUDY O'YOUNG, B.S.

SUMMARY Electrophysiological studies were performed in 22 patients with intraventricular conduction delay before and after intravenous infusion of disopyramide (Norpace), 2 mg/kg. Mean control maximal sinus node recovery time (1039 ± 187 msec), atrioventricular nodal conduction time (113 ± 28 msec), and atrioventricular nodal effective refractory periods (349 ± 67 msec) did not change significantly after administration of disopyramide (1073 ± 284 msec, 112 ± 31 msec, and 342 ± 42 msec, respectively). Mean spontaneous cycle length (756 ± 146 msec) decreased significantly 5 minutes after disopyramide (717 ± 124 msec) (p < 0.05), but not after 30 minutes (734 ± 142 msec). A small but statistically significant (p < 0.05) increase occurred after disopyramide in the mean atrial effective refractory period (259 ± 51 to 280 ± 53 msec), ventricular effective refractory period (253 ± 23 to 275 ± 33 msec), as well as the relative refractory period of the ventricular specialized conduction system (six patients) (433 ± 78 to 479 ± 62 msec). Although mean control infranodal conduction time (67 ± 35 msec) increased 5 minutes after disopyramide (79 ± 41 msec) (p < 0.001) (18%), no spontaneous episodes of second-degree or third-degree atrioventricular block were observed. In six patients with premature ventricular depolarizations (≥1/min), the arrhythmia was totally abolished in four, markedly reduced in one, and remained unchanged in one. Disopyramide resulted in significant prolongation of infranodal conduction time as well as in atrial and ventricular refractoriness, but nevertheless appears to be safe in patients with bundle branch block.

DISOPYRAMIDE PHOSPHATE (Norpace) is effective for treatment of cardiac arrhythmias. In vitro microelectrode studies have shown that this agent has electrophysiological properties similar to quinidine. Electrophysiological studies in animals showing that disopyramide is associated with prolongation of atrial and ventricular refractoriness as well as atrioventricular (AV) conduction are consonant with these observations. Recent studies of disopyramide in man have generally demonstrated increased atrial and ventricular refractoriness and variable effects on AV conduction. The various effects of disopyramide have been attributed to both direct and vagolytic actions. The reported prolongation of infranodal conduction time in several clinical studies prompted the suggestion that this agent is contraindicated in patients with intraventricular conduction disturbances. No comprehensive study of this drug in patients with AV or intraventricular conduction delay is currently available. In this study we assessed the electrophysiological effects and safety of intravenous disopyramide in patients with bundle branch block.

Materials and Methods

Twenty-two patients with right or left bundle branch block and recent acute myocardial infarction or those showing second or third degree AV block before study. These studies were performed according to protocol approved by the Committee of Human Experimentation of the University of California, San Francisco.

All studies were performed in the cardiac catheterization laboratory with the patients in a non-sedated, postabsorptive state. All cardiac drugs were terminated within three half-lives of those agents (except for one instance in which procainamide was inadvertently continued until 18 hours before study). Two multipolar electrode catheters were inserted into the right femoral vein: One catheter was positioned against the high right atrium for atrial pacing and recording while the other was positioned across the tricuspid valve for His bundle recordings. Surface leads X, Y, and Z of the Frank orthogonal lead system were continuously displayed simultaneously with those of the intracardiac electrogoms and recorded on a DR-12 Electronics for Medicine recorder. In 12 patients, ventricular pacing was instituted by manipulation of the right atrial catheter into the apex of the right ventricle. AV conduction was assessed using standard techniques, and cardiac refractory periods were determined with the extrastimulus technique. Atrial pacing was not possible in three patients because of atrial fibrillation (nos. 5, 13 and 18). Three patients (nos. 3, 10 and 19) did not undergo premature atrial stimulation (PAS), and AV refractory periods could not be measured in another (no. 21) because the His bundle was not consistently registered during PAS.

Study Protocol

After 20 minutes of stabilization, control recordings of heart rate, blood pressure, and AV nodal (A-H) and H-Q conduction were obtained. In addition, continu-
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<th>H-Q (msec)</th>
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* indicates patients with hypertension; † indicates patients with cardiomyopathy; ‡ indicates patients with Bundle Branch Block.
ous electrocardiographic recordings were made to assess the frequency of ventricular premature depolarizations. Atrial overdrive pacing was instituted beginning at cycle lengths approximately 50 msec below the spontaneous cycle length, and the paced cycle length was decreased by 50 msec decrements until AV nodal Wenckebach conduction was achieved. The sinus node recovery time (SNRT) and abnormalities in postspacing cycle lengths (2-10, secondary pause) were determined after 1 minute of pacing at each paced cycle length as described previously.14 Progressively premature atrial depolarizations at 10 msec decrements were inserted (Bloom Programmable Stimulator, Bloom and Associates, Warketh, PA) throughout the atrial diastolic cycle at paced cycle lengths of 500 msec. Twelve patients underwent both ventricular overdrive pacing and premature ventricular stimulation as just described. After completion of control observations, 2 mg/kg of disopyramide were infused intravenously over 7 minutes. (Blood disopyramide concentrations in the 2-4 μg/ml range were considered therapeutic.25, 26) Five minutes after completion of the infusion, heart rate, blood pressure, A-H, H-Q, and serum disopyramide levels were measured. Atrial (16 patients) and ventricular (12 patients) pacing studies were repeated beginning 10 minutes after termination of the infusion and were completed within 30 minutes. Heart rate, blood pressure, A-H, H-Q, and serum levels of disopyramide were again measured 30 minutes after termination of the infusion. The data were analyzed using the t test for paired data.

Definitions

The A-H interval was measured from the initial rapid deflection of the low right atrial electrogram to the initial deflection of the His bundle depolarization (normal range 60-120 msec).

The H-Q interval was measured from the initial His deflection to the earliest onset of ventricular activation detected on the surface electrogram (normal range 35-55 msec); S1S2 refers to the driven cycle length, and S2 refers to the premature stimulus.

The functional refractory period of atrium is defined as the shortest attainable A1A2 for any S1S2.

The effective refractory period of atrium is defined as the longest S1S2 that does not result in atrial depolarization.

The functional refractory period of the AV node is defined as the shortest H1H2 interval resulting from any two consecutive propagated atrial depolarizations.

The effective refractory period of the AV node is defined as the longest A1A2 interval at which A2 does not propagate to the His-Purkinje system.

The relative refractory period of the His-Purkinje system is defined as the longest H1H2 interval at which H2 conduct to the ventricle with a longer H-Q interval than that of the basic drive beat or with a QRS of aberrant morphology.

The effective refractory period of the His-Purkinje system is defined as the longest H1H2 interval at which H2 fails to depolarize the ventricles. The His-Purkinje system was considered as a single functioning unit for the purpose of this study.

The effective refractory period of ventricle is defined as the longest S1S2 interval during ventricular pacing with ventricular premature depolarization at which S2 fails to produce a ventricular depolarization.

Results

The relevant clinical and electrophysiological data are summarized in tables 1 and 2.

Sinus Function and Atrial Refractoriness

The mean control spontaneous cycle length (756 ± 146 msec) decreased significantly 5 minutes...
Table 2. Effects of Disopyramide on Sinus Node Recovery Time, Atrioventricular Nodal Conduction, and Cardiac Refractory Periods

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Mean ± SD: Control 1039 ± 187, 392 ± 94, 289 ± 43, 259 ± 51, 447 ± 77, 349 ± 67, 433 ± 78, 253 ± 23, 275 ± 33

*p Value

| NS | NS | <0.01 | <0.01 | NS | NS | <0.05 | <0.05 |

*His bundle depolarization not recorded.
†Infranodal Wenckebach.

Abbreviations: Max SNRT = maximal sinus node recovery time; Wenckebach = paced cycle length at which Wenckebach conduction occurred; AFRP = functional refractory period of atrium; AERP = effective refractory period of atrium; AVNFRP = functional refractory period of atrioventricular node; AVNERP = effective refractory period of atrioventricular node; RRP of HPS = relative refractory period of His-Purkinje system; VERP = ventricular effective refractory period.
after termination of disopyramide (717 ± 124 msec) 
\((p < 0.05)\), but was not significantly different 
(734 ± 142 msec) 30 minutes after infusion. Pro-
nounced decreases in spontaneous cycle length (> 120 
msec) were observed in only two patients. The mean 
spontaneous ventricular rate 5 minutes after infusion 
decreased in two and increased in one of the three 
patients with atrial fibrillation. Similarly, there was no 
significant change in the mean maximal SNRT 
(1039 ± 187 msec) after disopyramide (1073 ± 284 
msec) in 19 patients who were in sinus rhythm during 
the study.

Two of the 19 patients who underwent atrial over-
drive pacing had abnormalities in sinus node function. 
In patient 2, control studies showed prolonged maximal 
SNRT and secondary pauses; both of these ab-
normalities were abolished after disopyramide. In 
contrast, in the other patient (no. 3) maximal SNRT 
became markedly abnormal and secondary pauses 
persisted after disopyramide.

Atrial effective refractory periods were measured in 
16 of the 22 patients. Mean control atrial effective 
refractory period was 259 ± 51 msec and increased 
(280 ± 53 msec) significantly after disopyramide 
\((p < 0.05)\). Similarly, mean control atrial functional 
refractory period (289 ± 43 msec) increased 
(325 ± 49 msec) after disopyramide infusion 
\((p < 0.01)\).

**AV Conduction and Refractoriness**

Control A-H intervals were within normal limits in 
14 patients, abnormal (>120 msec) in five, and could 
not be determined in three due to atrial fibrillation. 
There was no significant change from mean control 
A-H (113 ± 28 msec) either 5 minutes (112 ± 31 
msec) or 30 minutes (112 ± 30 msec) after drug 
infusion. The A-H interval decreased in three patients and 
increased in two of the five patients who had 
prolonged control A-H intervals. There was no signifi-
cant change in mean paced atrial cycle length at which 
AV nodal Wenckebach occurred (392 ± 94 msec) 
after disopyramide (388 ± 82 msec).

Control AV nodal refractory periods could be 
determined in 13 of the 15 patients undergoing PAS. 
In two patients, these measurements were limited by 
atrial refractoriness. After disopyramide, the AV 
nodal effective refractory period could be determined 
in only seven of 15 patients, being limited by the atrial 
refractoriness in eight subjects. There was no signifi-
cant change in either AV nodal effective (349 ± 67 
msec) or functional refractory (447 ± 77 msec) 
periods after disopyramide (342 ± 42 and 419 ± 64 
msec, respectively).

**Infranodal Conduction and Refractory Periods**

Mean control H-Q interval was abnormally 
prolonged in 13 of 22 patients (55–210 msec). For the 
group as a whole, mean control H-Q (67 ± 35 msec) 
increased by 18% 5 minutes after disopyramide 
(79 ± 41 msec) \((p < 0.001)\). Thirty minutes after dis-
opyramide, mean H-Q (75 ± 36 msec) decreased 
slightly compared with the 5-minute determination 
\((p < 0.02)\) (fig. 1), but was still significantly greater 
than the control valve \((p < 0.001)\). There was no 
significant difference in either the absolute or mean 
percent H-Q increment after disopyramide between 
patients with normal H-Q intervals compared with 
patients with prolonged H-Q intervals. No sponta-
neous progression to second or third degree AV block 
was observed after disopyramide even in patients with 
marked prolongation of infranodal conduction time 
(fig. 2). Similarly, mean maximal H-Q during atrial 
overdrive pacing was significantly greater (24%) after 
disopyramide (91 ± 49 msec) compared with the max-
imal control H-Q during atrial overdrive pacing 
(74 ± 38 msec) \((p < 0.001)\). In one patient, atrial

\[\text{FIGURE 1. Effects of intravenous administration of disopyramide, 2 mg/kg, on infranodal conduction (H-Q) in 22 patients with intraventricular conduction delay at 5 and 30 minutes after infusion. Maximal H-Q prolongation is seen 5 minutes after infusion.}\]
overdrive pacing resulted in infranodal Wenckebach and 2:1 infranodal block after disopyramide (fig. 3).

His-Purkinje Refractory Periods

The relative refractory period of the His-Purkinje system could be compared before and after disopyramide in six of the 15 patients who underwent premature atrial stimulation. In the others, this parameter could not be determined either because atrial or AV nodal refractoriness was reached before that of the His-Purkinje system. The relative refractory period of the His-Purkinje system increased in all subjects (table 2), and the mean value was significantly greater after disopyramide (479 ± 62 msec) than the mean control value (433 ± 78 msec) (p < 0.05). The effective refractory period of the His-Purkinje system could not be determined in any of the subjects.

Ventricular Pacing Studies

Twelve of the 22 patients underwent ventricular overdrive pacing to assess the effects of disopyramide on retrograde ventriculoatrial conduction as well as ventricular refractoriness. In five subjects, ventriculoatrial dissociation was present at the longest paced cycle lengths (approximately 50 msec less than the spontaneous cycle length) both before and after disopyramide. Retrograde ventriculoatrial conduction was essentially unchanged after disopyramide in five and improved in one. The ventricular effective refractory period increased in 10 of the 12 patients, was unchanged in one and decreased in one. Mean control ventricular effective refractory period (253 ± 33 msec) increased significantly (275 ± 33) after disopyramide infusion (p < 0.05).

Intraventricular Conduction

Mean control QRS duration (159 ± 18 msec) increased significantly 5 minutes after disopyramide (175 ± 21 msec) (p < 0.001) and then decreased 30 minutes after disopyramide (169 ± 22), but was still significantly (p < 0.02) greater than control values (p < 0.005). There was no significant correlation between the absolute percent increment in QRS duration and control
QRS measurements, type of bundle branch block pattern, or peak disopyramide serum concentration.

**Disopyramide Serum Levels**

Serial serum concentrations of disopyramide were measured before and 5 and 30 minutes after drug infusion in 21 of the 22 patients. Mean peak disopyramide concentration (5.1 ± 2.2 μg/ml) occurred 5 minutes after drug administration, and subsequent disopyramide concentrations remained within the reported therapeutic range (2-4 μg/ml) throughout the study period in all but four patients in whom blood drug concentrations were slightly below 2 μg/ml at 30 minutes (table 1, fig. 4). There was no correlation between measured serum concentrations of drug and changes in H-Q or QRS duration either at 5 or 30 minutes after infusion.

**Arrhythmias**

The effects of disopyramide on premature ventricular depolarizations were assessed in six of 22 patients (premature ventricular depolarizations ranged from 1-54/min). Premature ventricular depolarizations were completely abolished in four, markedly decreased in one (from 54/min to 4/min), and unchanged in one. In one patient with right bundle branch block, progressively premature ventricular depolarizations during control studies resulted in a single reentrant ventricular depolarization; after disopyramide induced premature ventricular depolarizations, a series (up to six) of reentrant ventricular depolarizations occurred (fig. 5). However, no spontaneous increase in premature ventricular depolarizations or episodes of ventricular tachycardia were noted in this patient after disopyramide.

There was no significant change in blood pressure 5 or 30 minutes after disopyramide administration. In patient 8, severe nausea, emesis, and hypotension developed 5 minutes after disopyramide infusion; the hypotension was transient and required no specific therapy and was believed to represent a vasovagal reaction.

**Discussion**

Our study clearly establishes the safety of intravenously administered disopyramide in doses designed to achieve therapeutic serum concentrations in...
patients with bundle branch block. Mean maximal prolongation of H-Q was 18% greater than control values 5 minutes after drug infusion, and H-Q tended to return toward control values after 30 minutes. No spontaneous episodes of second degree or third degree AV block were recorded even in patients with markedly prolonged control H-Q intervals (fig. 1). In addition, there was no correlation between baseline H-Q, bundle branch block pattern, QRS duration, or serum disopyramide level and the H-Q increment after disopyramide. In contrast to our previous studies of procainamide in which a substantial lag was often observed between H-Q prolongation and serum blood levels, the data for disopyramide suggest that this drug rapidly equilibrates with cardiac tissue producing maximal effects within minutes after drug infusion.

Comparison with Previous Studies

The results of the present study are compared with previously published clinical electrophysiological data in table 3. Our work confirms the observations of Josephson et al.,26 Befeler et al.,26 Birkhead and Vaughan Williams,30 and Marrott et al.21 in that disopyramide results in small but statistically significant increases in atrial or ventricular effective refractory periods. Cardiac refractory periods in the present study were obtained in only 16 of the 22 patients. These findings differ from the observations of Befeler et al.,26 who found no significant change in atrial refractoriness after disopyramide. The variable effect of disopyramide on heart rate, SNRT, AV nodal conduction and refractory periods is best explained by both its direct and vagolytic actions, as emphasized by previous authors.30

Our findings relating to small but significant increases in H-Q support previous observations by Marrott et al.21 In the studies by Josephson et al.,26 Befeler et al.,26 Birkhead and Vaughan Williams,30 no significant change in H-Q was observed, although some patients in these studies showed an increase in this parameter. The differences between studies may be related to the relatively small patient sample size or differences in disopyramide dosings or both (table 3). Data relative to the effects of disopyramide on His-Purkinje refractory periods are few. Josephson et al.26 (table 3) found that the relative refractory period of the His-Purkinje system increased in the two patients in whom serial measurements could be obtained. Befeler et al.26 described no significant change in the relative refractory period of the His-Purkinje system, but neither the magnitude of the relative refractory period nor the number of patients in whom serial measurements could be obtained was mentioned. In our study, the relative refractory period of the His-Purkinje system increased in all six patients in whom several measurements could be compared (table 3).

Comparison with Other Antiarrhythmic Agents

Our findings support the concept that the electrophysiological effects of disopyramide in man are similar to those of other so-called type I antiarrhythmic agents (quinidine,37, 39, 40 procaainamide,37, 39, 40 and ajmaline41), in that atrial, His-Purkinje system, and ventricular refractoriness were prolonged as was infranodal conduction time. In addition, the degree of prolongation of the H-Q interval (18%) was similar to that (17%) found for a roughly comparable group of patients with bundle branch block who were studied with intravenous procainamide.37 A previous study of the electrophysiological effects of intravenous administration of quinidine in patients with bundle branch block in our laboratory showed no significant change in the H-Q interval after drug infusion.42 This study was limited in that hypotension (often pronounced) developed in most of the patients and the observed effects were an admixture of direct effects and

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**Figure 4.** Disopyramide blood concentrations (µg/ml) 5 and 30 minutes after intravenous infusion of 2 mg drug/kg in 20 patients with intraventricular conduction delay. The vertical lines represent the mean and standard deviation of disopyramide blood concentrations at 5 and 30 minutes.
those related to increased sympathetic tone. Other studies in which quinidine was administered intramuscularly showed significant prolongation of the H-Q interval. In contrast, previous studies of lidocaine, phenytoin, and propranolol showed that these agents produced no significant effects on the H-Q interval in patients with or without bundle branch block. The observed increases in the H-Q interval after disopyramide infusion were small and probably clinically insignificant.

### Table 3. Comparison of Studies of Electrophysiological Effects of Disopyramide in Man

<table>
<thead>
<tr>
<th>Authors</th>
<th>No. of patients</th>
<th>Dose (mg/kg)</th>
<th>A-H</th>
<th>H-Q</th>
<th>AERP</th>
<th>AVNERP</th>
<th>RRP of HPS</th>
<th>VERP</th>
<th>R-R</th>
<th>SNRT</th>
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<tr>
<td>Josephson et al.</td>
<td>12</td>
<td>1–2</td>
<td>→</td>
<td>→</td>
<td>↑</td>
<td>↓</td>
<td>*</td>
<td>→</td>
<td></td>
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</tr>
<tr>
<td>Befeler et al.</td>
<td>10</td>
<td>2</td>
<td>→</td>
<td>→</td>
<td>→</td>
<td>→</td>
<td>→</td>
<td>→</td>
<td></td>
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<tr>
<td>Spurrell et al.</td>
<td>10</td>
<td>2</td>
<td>→</td>
<td>→</td>
<td>↑</td>
<td>→</td>
<td>↑</td>
<td>→</td>
<td></td>
<td>↑</td>
</tr>
<tr>
<td>Birkhead and</td>
<td>14</td>
<td>2</td>
<td>↑</td>
<td>→</td>
<td>↑</td>
<td>→</td>
<td>→</td>
<td></td>
<td>↑</td>
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<tr>
<td>Vaughan Williams</td>
<td>10</td>
<td>1.5</td>
<td>→</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
<td>→</td>
<td></td>
<td></td>
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<tr>
<td>Marrott et al.</td>
<td>12</td>
<td>1.5</td>
<td>→</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
<td>→</td>
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<td></td>
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<tr>
<td>Present study</td>
<td>22</td>
<td>2</td>
<td>↑</td>
<td>↑</td>
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<td>↑</td>
<td>↑</td>
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</tbody>
</table>

*RRP of HPS was observed to increase in only two patients.
†Patients were studied after atropine administration in order to assess the direct effects of disopyramide.

Abbreviations: A-H = atrioventricular nodal conduction time; H-Q = His-Purkinje conduction time; AERP = effective refractory period of atrium; AVNERP = effective refractory period of atrioventricular node; RRP of HPS = relative refractory period of His-Purkinje system; VERP = ventricular effective refractory period; R-R = spontaneous cycle length; SNRT = sinus node recovery time; ↑ = increased (statistically significant); ↓ = decreased (statistically significant); → = no significant change.
Effects on Cardiac Arrhythmias

Therapeutic serum concentrations of disopyramide resulted in abolition or marked reduction in premature ventricular depolarizations in five of six patients with premature ventricular depolarizations.

The initiation of trains of reentrant ventricular depolarizations followed early induced premature ventricular depolarizations after disopyramide in one patient. This effect was probably related to the effect of this drug on ventricular conduction, as well as to its critical prolongation of conduction and refractoriness in the ventricular specialized conduction system allowing for repetitive reentrant ventricular depolarizations.29, 46-48 The absence of a retrograde His deflection during premature stimulation does not allow for distinction between His-Purkinje or ventricular reentry in this patient. In similar observations in their studies of the effects of procainamide on the His-Purkinje system reentry in man, Reddy et al.49 found that procainamide regularly resulted in repetitive reentry in eight of the 10 patients studied. No spontaneous increase in premature ventricular depolarizations or bouts of ventricular tachycardia were observed after disopyramide in any of the subjects.

Clinical Implications

Our study confirms the safety of intravenous disopyramide infusions in patients with bundle branch block (including those with marked infranodal conduction delay) in that no spontaneous episodes of AV block were observed. Similarly, limited observations in patients with prolonged A-H interval showed no significant deleterious effects of disopyramide on AV nodal conduction. These results were obtained in a group of hemodynamically stable patients and should not be extrapolated to acutely ill cardiac patients. For example, there are no available data regarding safety of disopyramide in patients with marked electrolyte abnormalities (especially hyperkalemia) or with concurrent use of other antiarrhythmic agents. Similarly, no data are available on the effects of this agent in patients with second or third degree AV block. In addition, this study does not address the important issue of the long-term safety of chronic oral disopyramide therapy, particularly for those patients with markedly prolonged infranodal conduction time. Finally, this drug must be used with caution in patients with sinus node dysfunction because some patients may have pronounced deterioration in sinus node function.49

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