Electrophysiologic Effects of Disopyramide in Patients with Atrioventricular Nodal Dysfunction

PETER R. WILKINSON, M.D., JAWAHAR DESAI, M.D., JAMES HOLLISTER, M.A., ROLANDO GONZALEZ, M.D., JOSEPH A. ABBOTT, M.D., AND MELVIN M. SCHEINMAN, M.D.

SUMMARY Seventeen patients with first-degree or Mobitz I atrioventricular (AV) block and narrow QRS complexes underwent electrophysiologic drug testing before and after i.v. administration of disopyramide. Disopyramide did not significantly change the mean sinus cycle length (895 ± 131 vs 877 ± 119 msec), mean maximal sinus node recovery time (1134 ± 169 vs 1133 ± 13 msec), mean atrial effective refractory period (314 ± 72 vs 307 ± 54 msec), mean AV nodal conduction time (187 ± 79 vs 180 ± 73 msec) or the mean paced cycle length at which AV nodal Wenckebach conduction occurred (545 ± 144 vs 497 ± 130 msec) after disopyramide. The mean AV nodal effective refractory period decreased significantly (from 535 ± 137 to 521 ± 122 msec), and both infranodal conduction time and the paced ventricular cycle length producing ventriculoatrial block increased significantly (from 56 ± 12 to 63 ± 13 msec and from 625 ± 158 to 655 ± 157 msec, respectively). We conclude that i.v. disopyramide administered in a dose resulting in therapeutic blood levels showed no adverse effects on AV nodal conduction in patients with AV nodal dysfunction. In contrast, i.v. disopyramide depressed retrograde AV conduction.

DISOPYRAMIDE phosphate (Norpace) has been used extensively for more than 10 years to treat atrial and ventricular arrhythmias;1-4 it has been approved in the United States for treatment of ventricular arrhythmias. As a class I antiarrhythmic agent, it decreases the amplitude and maximum upstroke velocity of the transmembrane action potential, prolongs its duration and slows the rate of rise of phase 4.5,6 Like other class I agents, it prolongs infranodal conduction time, although this does not appear to be clinically important when blood disopyramide levels are in the therapeutic range.7 The use of disopyramide in patients with first-degree or type I atrioventricular (AV) block and narrow QRS is not advised without suitable precautions,8 although in no previous studies have drug safety and efficacy been assessed. Previous studies in other patient populations have revealed a variable effect of disopyramide on AV nodal conduction and refractoriness, and this has been ascribed to the interplay of its membrane-depressant and anticholinergic actions.9-11 In the present study, we assessed the electrophysiologic effects and safety of i.v. disopyramide in patients with AV nodal dysfunction.

Methods

Patients entered into the study had been referred for electrophysiologic evaluation because of symptoms suggesting higher grades of AV block and surface electrocardiographic findings of first-degree (PR > 0.2 second) or Mobitz I (Wenckebach) AV block. These findings were confirmed in all patients during at least one 24-hour Holter recording. Patients were excluded if they had uncompensated cardiac failure, Mobitz II or third-degree AV block, renal impairment (serum creatinine > 2 mg/ml), myocardial infarction within the previous 4 months, a systolic blood pressure of less than 100 mm Hg or bundle branch block. The study was performed with the approval of the Committee on Human Research of the University of California, San Francisco, and each patient gave fully informed consent. The studies were performed at the University of California, San Francisco, and the Veterans Administration Medical Center, Fresno.

The patients were studied after having stopped all antiarrhythmic medications for four elimination drug half-lives. One to three surface ECG leads were recorded.

Two quadripolar pacing catheters were inserted via a femoral vein. One was advanced to the high right atrium and the other just across the tricuspid valve. The control sinus cycle length (CL) and AV nodal (AH) and infranodal (HQ) conduction times were measured.12 Simultaneous surface and intracardiac recordings were obtained using either a VR-12 Electronics for Medicine or a Hewlett-Packard Cath (Lab. 8890B) recorder. A programmable stimulator (Bloom and Associates) was used for intracardiac pacing studies. Control arterial blood pressure was measured twice, and blood samples were obtained for a control disopyramide assay. High right atrial (HRA) overdrive pacing was initiated with an initial CL of 50-msec less than the sinus CL, followed by 50-msec decrements until AV nodal Wenckebach block occurred. Each pacing run lasted 60 seconds, and the sinus node recovery time (SNRT) was measured after abrupt termination of pacing. Cardiac refractory periods were obtained by the extrastimulus techniques using a drive CL of either 500 or 600 msec.13 The HRA catheter was then repositioned against the apex of the right ventricle, and right ventricular overdrive pacing was initiated at a CL approximately 50 msec shorter than the sinus CL and was increased by 50 msec until ventriculoatrial block or ventriculoatrial dissociation occurred. The ventricular refractory period was measured by the extrastimulus technique at a basic paced CL of 500 msec. Disopyramide was then given by one of two regimens. Infusion 1 consisted of an infusion of 1.25 mg/kg over 15 minutes followed by 0.25 mg/kg
over 15 minutes. Blood pressure was measured 10, 15, 20 and 30 minutes after initiation of the infusion. Blood samples were taken at 10, 20, 30 and 60 minutes, and repeat electrophysiologic recordings were started immediately after the first infusion had ended. Infusion 2 involved a continuous infusion of 1 mg/kg/hour supplemented by boluses of 0.5 mg/kg each given over 5 minutes with 5-minute intervals between each. Infusion 1 yielded either subtherapeutic or low therapeutic blood levels; therefore, infusion 2 was used for the remaining subjects. Blood samples were taken to measure disopyramide levels before each bolus and 5 minutes after the last, and blood pressure was measured before and after each bolus to ensure that no significant hemodynamic deterioration had occurred. The repeat electrophysiologic measurements were started 5 minutes after the fourth bolus.

The data were analyzed using a paired two-tailed t test.

**Results**

Seventeen patients, mean age 64.2 years, were entered into the study. Twenty-four-hour continuous electrocardiographic recordings showed persistent first-degree AV block in all; five patients showed periods of type I AV block (table 1). Two of these five had spontaneous AV nodal Wenckebach conduction during the electrophysiologic study.

**AV Conduction and Refractoriness**

Control AV nodal conduction times were all prolonged, as expected. Disopyramide did not significantly change the AH interval, which was 187 ± 79 msec before and 180 ± 73 msec after disopyramide. Only patient 11 showed a significant increase in AH (70 msec) (fig. 1), but atrial overdrive pacing in this patient showed that AV nodal Wenckebach conduction occurred at the same paced atrial rate both before and after disopyramide (fig. 2). No patient developed higher grades of AV block during the study. In contrast, in two patients, the AH significantly decreased (by 90 msec in patient 2 and by 50 msec in patient 6). Patient 7 (fig. 3), who had AV nodal Wenckebach during control recordings, showed 1:1 conduction after disopyramide. The paced CL at which AV nodal Wenckebach occurred decreased from 545 ± 144 to 497 ± 130 msec after disopyramide. Patients 2, 5, 6, 11 and 17 had markedly prolonged AV nodal conduction times, ranging from 180 to 400 msec; none of these patients showed spontaneous AV nodal Wenckebach conduction after disopyramide.

AV nodal effective refractoriness could not be measured in eight patients: Two had spontaneous Mobitz I conduction, five had atrial refractoriness longer than that of AV node, and one patient developed atrial fibrillation after disopyramide. In the remaining patients, the AV nodal effective refractory periods decreased after disopyramide, from 535 ± 137 to 520 ± 122 msec (p < 0.05). Infranodal conduction time increased from 56 ± 12 msec to 63 ± 13 msec (p < 0.001). Control infranodal conduction time was markedly abnormal (90 msec) in patient 12, but increased by only 5 msec after disopyramide infusion. No patient showed pacing-induced infranodal block after disopyramide. In five of 17 patients, control ventricular overdrive pacing resulted in ventriculoatrial dissociation at the longest paced CL, while in two (patients 1 and 4), ventriculoatrial block occurred at the longest paced CL after disopyramide. Serial measurements of ventriculoatrial conduction were available in 10 patients and showed impaired retrograde conduction after disopyramide administration (625 ± 158 vs 655 ± 157 msec, p < 0.05).

**Disopyramide Serum Levels**

The mean disopyramide level at the conclusion of repeat electrophysiologic testing was 2.9 ± 0.9 µg/ml. Because the therapeutic range for disopyramide is considered to be 2.0–4.0 µg/ml, only two patients (nos. 4 and 5) had subtherapeutic blood levels of disopyramide at the time of repeat study; blood levels were not available in patient 2.

**Chronic Oral Disopyramide Therapy**

Patients 1, 6, 11, 16 and 17 had ventricular premature complexes frequent enough to warrant chronic

![Figure 1. Simultaneous recording of the Frank orthogonal lead system, X, Y and Z, high right atrial (HRA) and His bundle electrogram (HBE) from patient 11. (A) Control recordings showed marked prolongation of the atrioventricular nodal conduction time (AH = 230 msec). (B) After disopyramide, there is further significant prolongation of the AH interval (300 msec), but 1:1 atrioventricular conduction is maintained. Infranodal conduction time HQ increased from 55 to 65 msec, but the spontaneous cycle length (113 msec) is essentially unchanged. RV = right ventricular electrogram.](image-url)
oral disopyramide therapy. None had evidence of renal disease. The daily disopyramide dose ranged from 300 to 600 mg. These patients were followed for a mean of 7 ± 6 months (range 4 days to 16 months) and repeat ECG and one or more 24-hour continuous ECG recordings were obtained. No higher degrees of AV block were observed during chronic oral therapy and there was no significant change in the PR interval before (0.278 ± 0.062 msec) or during chronic oral therapy (0.270 ± 0.053 msec). Patient 1 had episodes of AV nodal Wenckebach conduction both before and after oral therapy. In two of the five patients, chronic therapy was discontinued because of the development of signs and symptoms of congestive heart failure 4 days and 2 weeks, respectively, after initiation of oral disopyramide. Both of these patients had a history of congestive heart failure but were well compensated at the time of study.

### Table 1. Clinical and Electrophysiologic Data

<table>
<thead>
<tr>
<th>Pt</th>
<th>24-hour ECG recordings</th>
<th>Serum disopyramide concentration† (μg/ml)</th>
<th>AH (msec)</th>
<th>HQ (msec)</th>
<th>QRS duration (msec)</th>
<th>AV nodal Wenckebach (msec)</th>
<th>AVNERP (msec)</th>
<th>VA block</th>
</tr>
</thead>
<tbody>
<tr>
<td>1‡</td>
<td>Mobitz I</td>
<td>2.1</td>
<td>W 50</td>
<td>110</td>
<td>WP 480</td>
<td>§</td>
<td>§</td>
<td>§</td>
</tr>
<tr>
<td>2</td>
<td>Mobitz I</td>
<td>1.0</td>
<td>W 40</td>
<td>110</td>
<td>700 NA §</td>
<td>§</td>
<td>§</td>
<td>§</td>
</tr>
<tr>
<td>3</td>
<td>Mobitz I</td>
<td>4.0</td>
<td>130 60</td>
<td>110</td>
<td>660 700</td>
<td>§</td>
<td>§</td>
<td>§</td>
</tr>
<tr>
<td>4</td>
<td>Mobitz I</td>
<td>1.0</td>
<td>160 55</td>
<td>100</td>
<td>680 680</td>
<td>§</td>
<td>§</td>
<td>§</td>
</tr>
<tr>
<td>5</td>
<td>Mobitz I</td>
<td>1.5</td>
<td>310 55</td>
<td>110</td>
<td>700 700</td>
<td>§</td>
<td>§</td>
<td>§</td>
</tr>
<tr>
<td>6</td>
<td>Mobitz I</td>
<td>1.0</td>
<td>180 60</td>
<td>110</td>
<td>660 660</td>
<td>§</td>
<td>§</td>
<td>§</td>
</tr>
<tr>
<td>7‡</td>
<td>Mobitz I</td>
<td>3.2</td>
<td>W 45</td>
<td>100</td>
<td>WP 90</td>
<td>§</td>
<td>§</td>
<td>§</td>
</tr>
<tr>
<td>8</td>
<td>Mobitz I</td>
<td>3.3</td>
<td>150 40</td>
<td>80</td>
<td>750 640</td>
<td>§</td>
<td>§</td>
<td>§</td>
</tr>
<tr>
<td>9</td>
<td>Mobitz I</td>
<td>2.9</td>
<td>170 75</td>
<td>90</td>
<td>400 340</td>
<td>§</td>
<td>§</td>
<td>§</td>
</tr>
<tr>
<td>10</td>
<td>Mobitz I</td>
<td>3.0</td>
<td>160 55</td>
<td>90</td>
<td>350 750</td>
<td>§</td>
<td>§</td>
<td>§</td>
</tr>
<tr>
<td>11</td>
<td>Mobitz I</td>
<td>4.7</td>
<td>235 50</td>
<td>80</td>
<td>750 690</td>
<td>§</td>
<td>§</td>
<td>§</td>
</tr>
<tr>
<td>12</td>
<td>Mobitz I</td>
<td>3.2</td>
<td>120 90</td>
<td>80</td>
<td>750 690</td>
<td>§</td>
<td>§</td>
<td>§</td>
</tr>
<tr>
<td>13</td>
<td>Mobitz I</td>
<td>3.0</td>
<td>160 60</td>
<td>80</td>
<td>350 750</td>
<td>§</td>
<td>§</td>
<td>§</td>
</tr>
<tr>
<td>14</td>
<td>Mobitz I</td>
<td>3.1</td>
<td>150 60</td>
<td>80</td>
<td>450 380</td>
<td>§</td>
<td>§</td>
<td>§</td>
</tr>
<tr>
<td>15</td>
<td>Mobitz I</td>
<td>3.2</td>
<td>130 60</td>
<td>80</td>
<td>450 410</td>
<td>§</td>
<td>§</td>
<td>§</td>
</tr>
<tr>
<td>16</td>
<td>Mobitz I</td>
<td>2.8</td>
<td>110 55</td>
<td>80</td>
<td>400 360</td>
<td>§</td>
<td>§</td>
<td>§</td>
</tr>
<tr>
<td>17</td>
<td>Mobitz I</td>
<td>2.1</td>
<td>245 45</td>
<td>50</td>
<td>600 560</td>
<td>§</td>
<td>§</td>
<td>§</td>
</tr>
<tr>
<td>Mean ± sd</td>
<td></td>
<td>2.9 ± 0.9</td>
<td>187 ± 79</td>
<td>56 ± 12</td>
<td>88 ± 16 545 ± 144</td>
<td>535 ± 137 § 625 ± 158</td>
<td>§</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>185 ± 72</td>
<td>63 ± 13</td>
<td>98 ± 17 497 ± 130</td>
<td>521 ± 122 § 655 ± 157</td>
<td>§</td>
<td></td>
</tr>
<tr>
<td>p</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>&lt; 0.001 NS</td>
<td>&lt; 0.001 NS</td>
<td>&lt; 0.05 &lt; 0.05</td>
</tr>
</tbody>
</table>

For each patient, the top value represents control and the bottom value represents disopyramide.

*Data on sinus nodal function (spontaneous cycle length and sinus node recovery time) as well as the atrial and ventricular effective refractory periods are available on request to the authors.

†Control disopyramide serum levels were < 0.1 μg/ml; listed values are those obtained just after completion of the repeat electrophysiologic studies.

‡Atrial overdrive pacing was not performed in patients 1 and 7, who showed spontaneous AV nodal Wenckebach conduction.

§VA block at longest paced ventricular cycle length.

†The atrial effective refractory period was longer than that of the AV node.

Abbreviations: AH = atrioventricular nodal conduction time; AVNERP = effective refractory period of atrioventricular node; HQ = His-Purkinje conduction time; NA = not available; SCL = spontaneous cycle length; VERP = ventricular effective refractory period; W = Wenckebach; WP = paced cycle length at which Wenckebach conduction occurred; VA = ventriculoatrial block.
Discussion

We found that therapeutic blood levels of disopyramide were safe in patients with AV nodal dysfunction. The effects of disopyramide on AV nodal conduction appeared to vary, but only one patient showed a significant increase in the AH interval and none showed progression to higher grades of AV block. Stressing AV nodal conduction by means of atrial overdrive pacing effected no significant change before or after drug infusion in the paced CL at which Wenckebach conduction was observed. These findings are of special importance because five patients had transient episodes of type I block on Holter recordings before the study and five patients had marked prolongation of the AH during control studies. One patient, in fact, showed AV nodal Wenckebach conduction during

FIGURE 2. Atrial overdrive pacing in patient 11 at a cycle length of 700 msec resulted in 3:2 atrioventricular nodal Wenckebach conduction both before (A) and after (B) disopyramide administration. Abbreviations are as in figure 1.

FIGURE 3. (A) Atrioventricular nodal Wenckebach conduction during the control recording. (B) After disopyramide, 1:1 atrioventricular conduction is present, although with an AH longer than that observed during the last conducted complex of the Wenckebach cycle. This could be due to marked proximal delay in the atrioventricular node after disopyramide, allowing distal portions to recover and conduct in a 1:1 fashion. The sinus rate (750 msec) remains constant during both readings. Abbreviations are as in figure 1.
PATIENT 11, who is reported to have severe AV nodal disease, showed marked increases in AV nodal conduction after disopyramide. This patient had a significant increase in AV nodal conduction, with a change of 20 ms in the AH interval. Our findings suggest that i.v. disopyramide may be safely administered to patients with AV nodal disease manifested by first-degree or type I AV block and narrow QRS complexes. The safety of chronic oral disopyramide must be tested in further clinical trials. Our preliminary data in five patients treated with chronic oral disopyramide suggest that the i.v. effects on AV conduction predict subsequent effects of short-term oral therapy. However, none of the patients showed obvious adverse hemodynamic effects during or after i.v. disopyramide, two developed signs and symptoms of congestive heart failure while on chronic oral therapy, suggesting that the hemodynamic response to i.v. administration may not predict the chronic oral response.

These findings should not be extrapolated to include patients with bundle branch block, because first-degree AV block or type I AV block may result from infranodal block. Finally, our study population had normal or minimally impaired cardiac function and the serum electrolytes were within normal limits. Our findings, therefore, cannot be extrapolated to seriously ill or unstable cardiac patients.

References
The Cellular Electrophysiologic Mechanism of the Dual Actions of Disopyramide on Rabbit Sinus Node Function

TAKAO KATOH, M.D., HRAYR S. KARAGUEUZIAN, PH.D., JAY JORDAN, M.D., AND WILLIAM J. MANDEL, M.D.

with the technical assistance of Avile McCullen

SUMMARY To determine the contribution of disopyramide's suggested opposing direct depressant and indirect acceleratory actions on sinus node function, we studied the effects of disopyramide, 1 x 10^-7 to 1 x 10^-4 M, on isolated rabbit sinus node preparations using standard microelectrode techniques. Transmembrane potentials were recorded simultaneously from the sinus node and adjoining crista terminalis area. Disopyramide, as much as 1 x 10^-5 M, had no effects on the sinus cycle length. At a concentration of 1 x 10^-4 M, sinus cycle length was significantly prolonged due to prolongation of the sinus nodal action potential duration. During cholinergic blockade with atropine, 1 x 10^-6 M, disopyramide, 1 x 10^-7 to 1 x 10^-4 M, significantly prolonged sinus cycle length as a result of a prolongation of the sinus nodal action potential duration and a decrease of the slope of phase 4 depolarization. During cholinergic stimulation with carbamyl choline, 1 x 10^-5 M, disopyramide, 1 x 10^-7 to 1 x 10^-4 M, tended to reverse carbamyl choline-induced prolongation of the sinus cycle length (NS). This acceleratory action of disopyramide was caused by a significant increase of the slope of phase 4 depolarization. Disopyramide, 1 x 10^-7 to 1 x 10^-4 M, had no significant effects on corrected sinus node recovery time or sinus atrial conduction time under any conditions studied. We conclude that disopyramide has a direct depressant action on normal sinus node cells at the upper therapeutic and toxic levels, which is enhanced during cholinergic blockade, and that disopyramide's acceleratory action appears only at much lower concentrations and only during cholinergic stimulation.

DISOPYRAMIDE is a useful antiarrhythmic agent that has significant effects against a variety of experimental \(^1\) and clinical \(^2\) arrhythmias of both atrial and ventricular origin.

Its spectrum of antiarrhythmic effects is similar to that of quinidine in rabbit right atria, \(^3\) canine Purkinje fibers \(^4\) and in the specialized conduction system in man. \(^5\) \(^6\) However, the mechanisms of electrophysiologic action of disopyramide on sinus node function in man are controversial. \(^7\) \(^8\) \(^9\) Birkhead and Vaughan Williams \(^10\) suggested that disopyramide has dual effects on sinus nodal automaticity, resulting in a potentially unpredictable effect on sinus node function. One effect was thought to be mediated by a direct depressant action of the drug on sinus node cells, causing a slowing of heart rate, and the other action to be mediated by disopyramide’s anticholinergic action (that is, atropine-like action), which would remove cholinergic inhibitory action, causing an acceleration of heart rate. These properties of disopyramide could similarly affect in a dual manner the sinus node recovery time. Therefore, the purpose of the present study was to test the hypothesis that disopyramide has dual actions on sinus nodal automaticity, and, if so, to determine the cellular mechanisms of the dual action. We used standard microelectrode techniques to record transmembrane potentials using isolated rabbit right atrial preparations before and after superfusion with disopyramide, under control (resting), activated and blocked cholinergic tone to determine the cellular electrophysiologic mechanisms of disopyramide’s actions on the sinus nodal pacemaker cells.

Methods

Rabbits that weighed 1.5–3 kg were stunned by a blow on the head. The hearts were then rapidly excised and dissected in cool, oxygenated, modified Tyrode’s
Electrophysiologic effects of disopyramide in patients with atrioventricular nodal dysfunction.

P R Wilkinson, J Desai, J Hollister, R Gonzalez, J A Abbott and M M Scheinman

Circulation. 1982;66:1211-1216
doi: 10.1161/01.CIR.66.6.1211

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/66/6/1211

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation is online at:
http://circ.ahajournals.org//subscriptions/