Electrophysiologic Effects of Disopyramide in Patients with Atrioventricular Nodal Dysfunction

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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, 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. 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. The use of disopyramide in patients with first-degree or type I atrioventricular (AV) block and narrow QRS is not advised without suitable precautions, 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. 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. The 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. 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

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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 mark-

![Figure 1](https://example.com) Simultaneous recording of the Frank orthogonal lead system, X, Y and Z, high right atrial (HRA) and His bundle electrogram (HBE) from patient 1. (A) Control recordings show 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.

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
TABLE 1. Clinical and Electrophysiologic Data

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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 override 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 = atioventricular 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.

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 I 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.
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
control recordings that reverted to 1:1 conduction after disopyramide (fig. 3).

Our findings are similar to those reported by Marrott et al., Birkhead and Vaughan Williams, and Spurrell et al. in that varied and minor changes were noted in AV nodal conduction and refractory periods in patients with normal AV nodal function. Josephson et al. found a variable effect of disopyramide on AH and an increase in AV nodal effective refractory period from 256 to 269 msec. Befeler et al. included three patients with first-degree AV block in their study of 10 patients with cardiac disease and found no change in AV nodal conduction or refractoriness. However, the disopyramide levels that they achieved were almost always < 2 μg/ml, which is below the accepted minimal therapeutic blood level. The most likely explanation for the varied effects of disopyramide on AV nodal conduction and refractoriness relates to the interplay between direct and vagolytic actions of this drug on AV nodal function. In contrast to the varied effects of this drug on antegrade AV conduction, retrograde ventriculoatrial conduction showed definite deterioration. The exact size of retrograde block could not be determined because the His bundle deflection could not be recorded during ventricular pacing. However, our findings are similar to those of Shenasa et al., who described varying effects on antegrade but impaired retrograde AV nodal conduction after procainamide in patients without supraventricular tachycardia. Our findings are in accord with those of Swiryn et al., who found uniform depression of ventriculoatrial conduction in patients with either AV nodal or AV reentrant tachycardia after treatment with oral disopyramide. In contrast to our study (and to other studies of patients without PSVT), they also found uniform depression of antegrade AV nodal conduction. The differences may be related to differing AV nodal responses to this drug in patients with paroxysmal supraventricular tachycardia. In addition, we administered i.v. disopyramide, while Swiryn et al. restudied the patients after oral disopyramide. The latter approach could result in more direct suppression of antegrade AV nodal conduction.

Our study also emphasizes the limitations in the use of changes in the PR interval as a reflection of AV nodal function in patients treated with disopyramide. Patient 11, for example, showed marked increases in the AH interval after disopyramide without significant changes in AV nodal conduction or refractoriness. In addition, disopyramide usually prolongs infranodal conduction and, hence, may lengthen the PR interval without affecting AV nodal function.

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. In contrast, although 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

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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, $1 \times 10^{-7}$ to $1 \times 10^{-4} \text{M}$, 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 $1 \times 10^{-5} \text{M}$, had no effects on the sinus cycle length. At a concentration of $1 \times 10^{-4} \text{M}$, sinus cycle length was significantly prolonged due to prolongation of the sinus nodal action potential duration. During cholinergic blockade with atropine, $1 \times 10^{-6} \text{M}$, disopyramide, $1 \times 10^{-7}$ to $1 \times 10^{-4} \text{M}$, 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, $1 \times 10^{-5} \text{M}$, disopyramide, $1 \times 10^{-7}$ to $1 \times 10^{-4} \text{M}$, 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, $1 \times 10^{-7}$ to $1 \times 10^{-4} \text{M}$, had no significant effects on corrected sinus node recovery time or sinoatrial 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 experimental1, 2 and clinical3–7 arrhythmias of both atrial and ventricular origin.

Its spectrum of antiarrhythmic effects is similar to that of quinidine in rabbit right atria,8 canine Purkinje fibers9–11 and in the specialized conduction system in man.12, 13 However, the mechanisms of electrophysiologic action of disopyramide on sinus node function in man are controversial.13–16 Birkhead and Vaughan Williams15 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
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P R Wilkinson, J Desai, J Hollister, R Gonzalez, J A Abbott and M M Scheinman

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