Effects of Disopyramide on Electrophysiological and Mechanical Properties of the Heart

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Abstract ☐ Studies were performed in whole dog and in isolated superfused canine Purkinje fiber–papillary muscle preparations to investigate mechanisms responsible for the antiarrhythmic effects of disopyramide. Two human left atrial appendages were also studied *in vitro*. Disopyramide had a potent quinidine-like effect which may explain the antiarrhythmic properties of disopyramide. While disopyramide is perhaps at least twice as potent as quinidine in suppressing experimentally induced arrhythmias, disopyramide also has at least *proportionally more* depressant effect on cardiac mechanical performance in the dog heart.

Keyphrases ☐ Disopyramide—effects on electrophysiological and mechanical properties of the heart, *in vitro, in vivo* ☐ Antiarrhythmic activity, disopyramide—effects on electrophysiological and mechanical properties of the heart, *in vitro, in vivo* ☐ Quinidine-like activity—effects of disopyramide on *in vitro* and *in vivo* electrophysiological and mechanical properties of the heart ☐ Cardiac effects, electrophysiological and mechanical—disopyramide

The use of quinidine and quinidine-like drugs in the treatment of both supraventricular and ventricular arrhythmias, due to a variety of etiologies, remains one basic form of therapy for cardiac arrhythmias. The pharmacology of a new antiarrhythmic agent disopyramide[1], [2-(diisopropylamino)ethyl]-α-phenyl-2-pyridineacetamide, has been compared with that of quinidine (1). It was found that disopyramide was at least twice as potent as quinidine in abolishing arrhythmias induced experimentally by repetitive electrical stimulation, by local application of aconitine nitrate, by coronary artery ligation, and by ouabain infusion. The acute toxicity of disopyramide was reported to be relatively low, the intravenous therapeutic ratio in dogs being about 10 (1).

These data led to limited clinical trials of disopyramide (2). According to Katz *et al.* (2), disopyramide converted 11 of the 19 subjects with various arrhythmias to normal sinus rhythm; two patients (one with chronic atrial fibrillation and one with frequent premature ventricular contractions) who did not respond to quinidine therapy were subsequently converted by disopyramide at doses less than 50% of the quinidine dosage. At present, larger scale clinical trials of disopyramide are underway[2]. This paper reports the effects of disopyramide on the electrophysiological properties of the dog heart and human atrial tissue to elucidate the antiarrhythmic actions of disopyramide. Also the effects of disopyramide on canine cardiac mechanical performance were evaluated so that the effects of disopyramide on the electrophysiological and mechanical parameters in the dog heart could be correlated.

EXPERIMENTAL

In Vivo Studies—The cardiac effects of intravenous injections of disopyramide were evaluated in six adult mongrel dogs anesthetized with sodium pentobarbital (30 mg./kg.) and maintained on controlled respiration. Arterial blood pressure was recorded continuously using a transducer[3]. An electrode catheter was introduced into the right atrium for pacing and recording. His bundle electrograms were recorded by use of another bipolar electrode catheter positioned near the A–V node as previously described (3). Thus, the A–V conduction time could be divided into three time segments: intraatrial, A–V nodal, and intraventricular. Cardiac pacing at various rates was used to stress A–V conduction. The effects of right vagal stimulation (2 msec., 5 v., 20 Hz.) on sinus rate, A–V conduction, and ventricular automaticity were also evaluated in each experiment.

A micromanometer catheter was introduced into the left ventricle *via* a common carotid artery for recording intraventricular pressure. Left ventricular dP/dt was obtained using an operational amplifier. In addition, a strain-gauge arch was sutured on the right ventricular wall for monitoring a representative segment of myocardial contractile force (4).

After control records were obtained during normal sinus rhythm and atrial pacing at various rates, disopyramide (10 mg./ml. dissolved in normal saline) was administered slowly by vein at a dose of 3 mg./kg. Serial recordings of sinus rate, A–V conduction, ventricular automaticity, blood pressures, left ventricular pressures and dP/dt, and myocardial segment contractility were monitored up to 2 hr. after drug injection.

Two hours after the injection of the first dose of disopyramide, a second dose of 5 mg./kg. was given to all animals. Thus, each animal received a cumulative dose of 8 mg./kg. of disopyramide. Serial recordings of sinus rate, cardiac conduction, ventricular automaticity, blood pressures, and ventricular mechanical performance were again obtained up to 2 hr. after the second dose of disopyramide.

In three dogs, the effects of the intravenous injection of quinidine, 5 and 8 mg./kg., were evaluated and compared to disopyramide injections.

In Vitro Studies—Seven canine Purkinje fiber–papillary muscle preparations and two human left atrial appendages (one obtained from a 56-year-old man who underwent coronary bypass surgery and the other obtained from a teen-aged boy who underwent corrective surgery for tetralogy of Fallot) were studied. Intracellular and extracellular recordings were obtained by conventional electrophysiological techniques under control conditions, during drug infusion (1 or 2 mg./l.), and after washing out the drug. Doses of disopyramide up to 2 mg./kg. have been used in man, and it was thought that the concentration range of the drug used in these studies would be within the clinical therapeutic level. The preparations were superfused with modified Tyrode's solution (K = 4.0 meq./l.) at 37°.

Table I—Effects of Disopyramide and Quinidine on Sinus Rate[a]

	Time after First Dose				Time after Second Dose		
	0 min.	3 min.	30 min.	120 min.	3 min.	30 min.	120 min.
Disopyramide group	151 ± 8	3 mg./kg. 117 ± 10**	129 ± 9*	135 ± 12*	114 ± 8+	5 mg./kg. 124 ± 9**	128 ± 9*
Quinidine group	132 ± 10	5 mg./kg. 129 ± 6	134 ± 11	140 ± 20	145 ± 19	8 mg./kg. 139 ± 22	140 ± 18

[a] Values are mean ± SE. * = $p < 0.05$; ** = $p < 0.01$; + = $p < 0.001$.

The preparations were driven at a fixed rate of between 60 and 100/min. in canine preparation and of between 30 and 60/min. in human atrial preparations. The refractory period and the membrane responsiveness were studied by applying an extra stimulus (with adjustable delays) during the repolarization phase of every 10th driven beat.

Statistical Analysis—Paired t tests were performed to determine changes induced by the drugs in the same preparation. Nonpaired t tests were used to determine whether the differences observed between two groups were statistically significant. The p-values were expressed as nonsignificant (>0.05) and significant at three levels (<0.05, <0.01, and <0.001).

RESULTS

In Vivo Studies—Effects of Disopyramide on Automaticity—A depression of sinus automaticity was noticed after disopyramide injection. Table I compares the effects of disopyramide and quini-
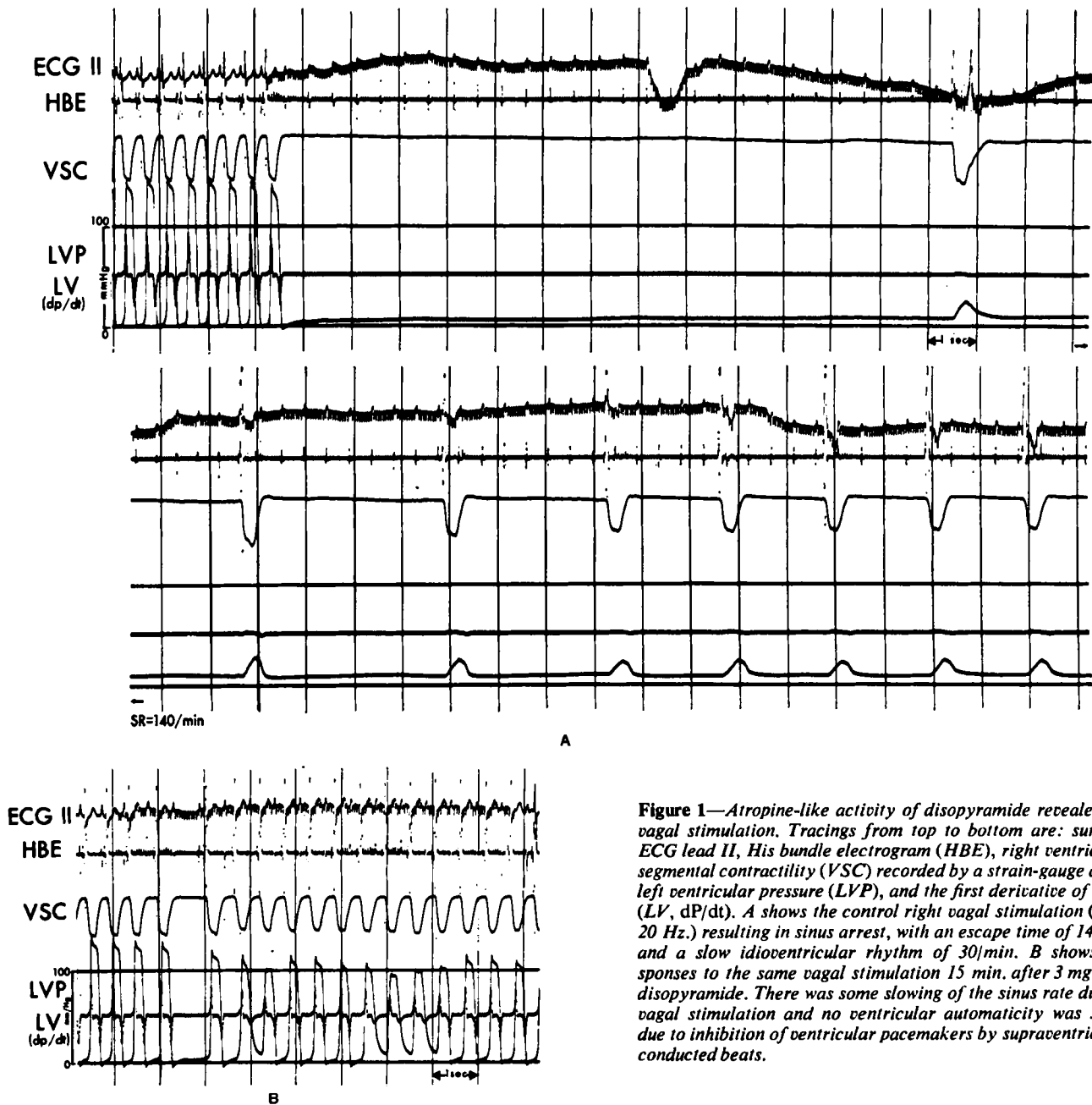

Figure 1—Atropine-like activity of disopyramide revealed by vagal stimulation. Tracings from top to bottom are: surface ECG lead II, His bundle electrogram (HBE), right ventricular segmental contractility (VSC) recorded by a strain-gauge arch, left ventricular pressure (LVP), and the first derivative of LVP (LV, dP/dt). A shows the control right vagal stimulation (5 v., 20 Hz.) resulting in sinus arrest, with an escape time of 14 sec. and a slow idioventricular rhythm of 30/min. B shows responses to the same vagal stimulation 15 min. after 3 mg./kg. disopyramide. There was some slowing of the sinus rate during vagal stimulation and no ventricular automaticity was seen, due to inhibition of ventricular pacemakers by supraventricular conducted beats.
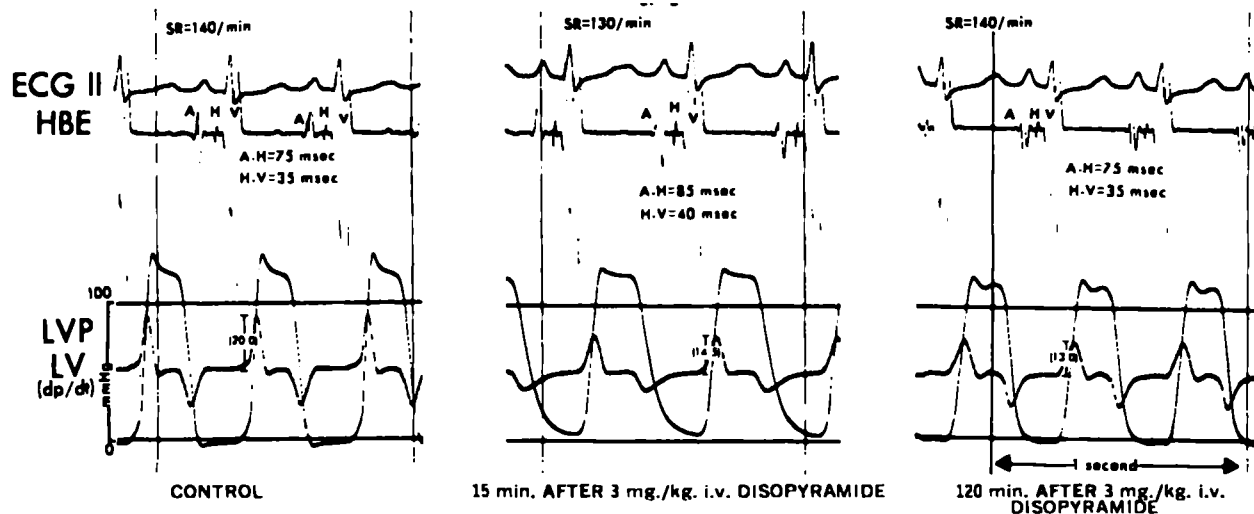
Figure 2 · *Effects of disopyramide on sinus rate, A–V conduction, and left ventricular pressures. The top tracing is surface ECG lead II. The labels in the His bundle electrogram (HBE) are: A, activation of atrial septum near the A V node; H, His bundle electrogram; and V, ventricular electrogram. The left panel is the control. Disopyramide, 3 mg./kg., caused some slowing of the sinus rate associated with A–V nodal and intraventricular conduction delay. Disopyramide also caused a decrease of systolic pressure and dP/dt and a rise in end diastolic pressure of the left ventricle. This dog recovered from the electrophysiological effects of disopyramide within 2 hr., while the depression of left ventricular mechanical performance was still evident.*

dine on sinus rate. It is evident that disopyramide had a greater depressant effect than quinidine on sinus automaticity and that this depressant effect lasted longer than 2 hr.

Disopyramide also had a much more potent vagolytic effect than quinidine. Ventricular automaticity could not be evaluated after disopyramide because vagal stimulation failed to cause sinus arrest (Fig. 1). This inhibition of the vagal effect on sinus automaticity by disopyramide lasted more than 2 hr. after a 3-mg./kg. i.v. injection of disopyramide. No such vagolytic effect was observed after administration of quinidine, even at the 8-mg./kg. dose.

Effects of Disopyramide on Cardiac Conduction—At both dose levels (3 and 5 mg./kg.), disopyramide caused significant conduction delay in both the A V node and the specialized ventricular conduction system, although there was an associated decrease in sinus rate (Figs. 2 and 3). The lower dose of quinidine (5 mg./kg.) had no effect on cardiac conduction; the higher dose (8 mg./kg.) caused a slight depression of both A V nodal and intraventricular conduction, which, however, was not as marked as those induced by 3 mg./kg. disopyramide. The depression of A-V nodal conduction lasted

somewhat longer than the depression of intraventricular conduction with both disopyramide and quinidine (8 mg./kg.). Table II summarizes the results obtained using His bundle recordings.

The direct depressant effect of disopyramide on A V conduction overwhelmed its vagolytic effect. Wenckebach cycles developed at a mean pacing rate of 340 beats/min. under control conditions and of 284 beats/min. 3 min. after 3 mg./kg. disopyramide. This depression of A-V nodal conduction persisted for about 1 hr. and disappeared by the end of the 2nd hr. Quinidine, 5 mg./kg., caused a similar qualitative depression of A V nodal conduction, but this effect was only revealed by pacing.

Effects of Disopyramide on Arterial Blood Pressure - No change in mean arterial blood pressure was noticed after the injection of 3 mg./kg. disopyramide. However, higher doses of disopyramide (5 mg./kg.) caused an average 11-mm. Hg decrease in mean blood pressure. Compared to "equiantiarrhythmic" doses, quinidine had a more potent depressor effect (a 16-mm. Hg decrease in mean blood pressure was noted after 5 mg./kg. quinidine) than disopyramide (Table III).
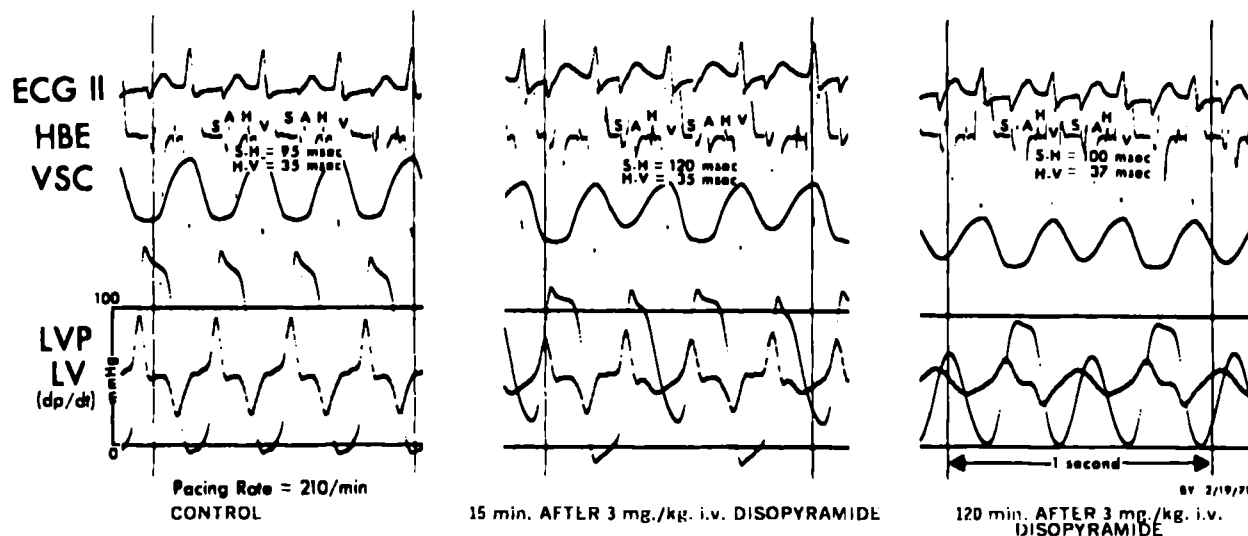

Figure 3- *Effects of 3 mg./kg. i.v. disopyramide on the dog heart. Comparisons were made with the heart rate controlled by atrial pacing at a fixed rate, 210/min. S is the stimulus artifact, and other labels are similar to those in previous figures. The left panel is the control. The middle panel shows the prolonged supraventricular conduction time (S–H interval) and depression of ventricular function (decrease in ventricular systolic pressure and dP/dt and alternate contractions) 15 min. after disopyramide injection. The right panel again shows the recovery of the depressant electrophysiological effects of disopyramide, with depression of ventricular mechanical performance remaining.*

Table II—Effects of Disopyramide and Quinidine on A-V Nodal and Intraventricular Conduction[a]

		Time after First Dose 0 min.	3 min.	30 min.	120 min.	Time after Second Dose 3 min.	30 min.	120 min.
		3 mg./kg.				**5 mg./kg.**		
Disopyramide	A-H	56 ± 2	70 ± 6**	64 ± 5**	61 ± 4	75 ± 6*	66 ± 4*	64 ± 4
group	H-V	34 ± 1	37 ± 2**	34 ± 2	31 ± 1	38 ± 2*	32 ± 1	32 ± 1
		5 mg./kg.				**8 mg./kg.**		
Quinidine	A-H	58 ± 2	58 ± 2	54 ± 1	53 ± 2	56 ± 5*	59 ± 1	64 ± 0
group	H-V	30 ± 0	30 ± 0	30 ± 0	30 ± 0	34 ± 1	29 ± 1	32 ± 1

[a] Values are mean ± SE in msec. * = $p < 0.05$; ** = $p < 0.01$.

Table III—Effects of Disopyramide and Quinidine on Mean Arterial Blood Pressure[a] (mm. Hg) in Anesthetized Dogs

	Time after First Dose 0 min.	3 min.	30 min.	120 min.	Time after Second Dose 3 min.	30 min.	120 min.
		3 mg./kg.				**5 mg./kg.**	
Disopyramide group	103 ± 9	102 ± 11	111 ± 9	116 ± 9	105 ± 10*	112 ± 10	111 ± 8
		5 mg./kg.				**8 mg./kg.**	
Quinidine group	115 ± 8	99 ± 10**	106 ± 6*	122 ± 4	107 ± 6**	113 ± 4*	117 ± 2

[a] * = $p < 0.05$; ** = $p < 0.01$.

Table IV—Effects of Disopyramide and Quinidine on Left Ventricular Pressures[a] (mm. Hg) and Maximum dP/dt (mm. Hg/sec.)

	Systolic Pressure Disopyramide Group	Quinidine Group	End Diastolic Pressure Disopyramide Group	Quinidine Group	dP/dt Disopyramide Group	Quinidine Group
Control	127 ± 9	103 ± 7	6 ± 3	5 ± 0	2020 ± 160	2050 ± 40
	3 mg./kg.	**5 mg./kg.**	**3 mg./kg.**	**5 mg./kg.**	**3 mg./kg.**	**5 mg./kg.**
3 min. after first dose	115 ± 9	111 ± 6*	8 ± 2*	8 ± 2	1370 ± 170**	1820 ± 88
30 min. after first dose	126 ± 5	118 ± 7*	8 ± 2	7 ± 1	1680 ± 90*	1700 ± 70
120 min. after first dose (second control)	128 ± 5	146 ± 1	5 ± 2	5 ± 4	1540 ± 120*	1950 ± 230
	5 mg./kg.	**8 mg./kg.**	**5 mg./kg.**	**8 mg./kg.**	**5 mg./kg.**	**8 mg./kg.**
3 min. after second dose	118 ± 7	130 ± 4*	10 ± 2*	5 ± 4	1100 ± 110**	1800 ± 200
30 min. after second dose	123 ± 6	147 ± 7	8 ± 3*	6 ± 4	1270 ± 140*	2100 ± 220
120 min. after second dose	120 ± 6	136 ± 1	8 ± 3	5 ± 2	1470 ± 180	2300 ± 200

[a] * = $p < 0.05$; ** = $p < 0.01$.

Effects of Disopyramide on Ventricular Performance—Both disopyramide and quinidine caused a depression in left ventricular systolic pressure and an increase in end diastolic pressure. These changes in left ventricular pressures lasted about 2 hr. Similar but less evident depression of ventricular contractility was observed with strain-gauge recordings (Fig. 3). Disopyramide was found to have a much more pronounced depressant effect than quinidine on the maximum dP/dt of the left ventricle. This depressant effect persisted longer than 2 hr. (Fig. 2). Thus, the depressant effect of disopyramide on cardiac mechanical performance persisted when the electrophysiological effects of the drug had disappeared (Table IV).

Depression of ventricular mechanical performance by disopyramide and quinidine was also demonstrated by pacing. The ability of the ventricular muscle to respond mechanically to pacing was impaired, and "pulsus alternans" developed at a lower driving rate after injection of the drugs (Fig. 3).

In Vitro Studies—Superfusion with Tyrode's solution containing disopyramide (1–2 mg./l.) significantly prolongated the action potential duration, decreased the rate of maximum depolarization (dV/dt) maximum, and caused conduction delay without significantly affecting the resting potential or the overshoot (Figs. 4 and 5). Therefore, the electrophysiological properties of disopyramide can be classified as "quinidine-like." The prolongation in action potential duration probably was the first electrophysiological change noted, and it became evident after 20 min. of superfusion with 1 mg./l. disopyramide. The maximal depressant effects of disopyramide were reached within 1 hr., and some drug effects

persisted even after a 30-min. washout period. Table V shows data obtained from one canine preparation.

Depression of electrophysiological parameters occurred earlier and was more pronounced when 2 mg./l. disopyramide was used. Qualitatively similar responses were seen in human atrial tissues, but the human atrial muscle fibers seemed to be more resistant to the depressant effects of disopyramide than were the canine Purkinje fibers (Fig. 6).

As expected, the membrane responsiveness curves were shifted to the right after perfusion with disopyramide. This shift in membrane responsiveness was also associated with a significant depression of maximum dV/dt after complete repolarization when higher doses of disopyramide were used (Fig. 7).

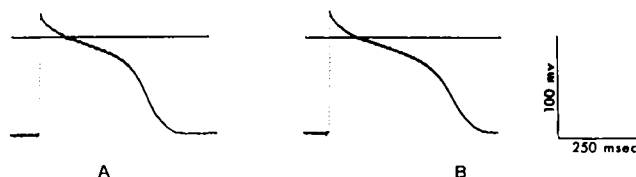No spontaneous automaticity was observed in human left atrial

Figure 4—*Effects of 1 mg./l. disopyramide on the action potential duration of a canine Purkinje fiber driven at a cycle length of 630 msec. The control (A) action potential duration was 400 msec. Thirty minutes after exposure to disopyramide (B), the action potential had increased to 450 msec.*

Table V—Electrophysiological Effects of 1 mg./l. Disopyramide on Canine Purkinje-Muscle Preparations[a]

	Resting Potential, mv.	Overshoot, mv.	Action Potential Amplitude, mv.	$(dV/dt)_{max}$, v./sec.	Conduction Time, Purkinje Fiber to Muscle, msec.	80% Action Potential Duration, msec.
Control	92 ± 1	25 ± 1	117 ± 1	670 ± 20	8.6 ± 1.6	302 ± 15
20 min. after disopyramide, 1 mg./l.	89 ± 2	27 ± 2	116 ± 2	604 ± 24	8.8 ± 1.4	343 ± 16
60 min. after disopyramide, 1 mg./l.	91 ± 1	28 ± 1	119 ± 1	462 ± 20	10.6 ± 1.2	429 ± 20
30 min. after washout	90 ± 1	27 ± 2	117 ± 1	559 ± 15	9.6 ± 1.4	378 ± 20

[a] The values are the mean ± SE for seven experiments.

preparations. The canine Purkinje-papillary muscle preparations also had slow spontaneous phase 4 depolarization, so the effects of disopyramide on automaticity could not be properly evaluated in these *in vitro* preparations. However, judging from the decrease in inward sodium current caused by the drug, disopyramide might have a depressant effect in preparations exhibiting a high spontaneous rate.

DISCUSSION

Disopyramide in doses of 3 or 5 mg./kg. i.v. caused a slowing of sinus rate in intact dogs, presumably through the decrease of the slope of phase 4 depolarization of sinoatrial pacemakers. Disopyramide, 1 or 2 mg./l., caused a shift of membrane responsiveness curves to the right. These direct quinidine-like properties of disopyramide are consistent with its clinical effectiveness in the suppression or abolition of arrhythmias due to enhanced phase 4 depolarization.

Disopyramide also prolonged action potential duration and increased the effective refractory period. Both effects of disopyramide can result in the abolition of premature "contractions"; if the premature depolarization reaches a refractory tissue, it will not elicit an effective response and the premature contraction will be suppressed. The prolongation of the action potential and refractory period could also account for a beneficial therapeutic response in arrhythmias resulting from reentrant mechanisms. Disopyramide would be effective if the slowing of conduction induced by the drug were proportionally less than the prolongation in the effective refractory period, *i.e.*, if the conduction speed in the circus pathway were relatively accelerated by the drug. In Purkinje-muscle preparations, disopyramide caused a greater prolongation of the refractory period than conduction velocity (*cf.*, Table V); thus, it may abolish arrhythmias caused by unidirectional conduction delay and reentry.

These data indicate that disopyramide is a quinidine-like drug, and its antiarrhythmic properties could be explained on the basis of: (*a*) a possible depression of unduly enhanced phase 4 depolarization, (*b*) decreased membrane responsiveness, and (*c*) prolongation of the refractory period.

The electrophysiological effects of disopyramide obtained from our microelectrode studies are qualitatively similar to those reported by Sekiya and Vaughan Williams (5). However, quantita-
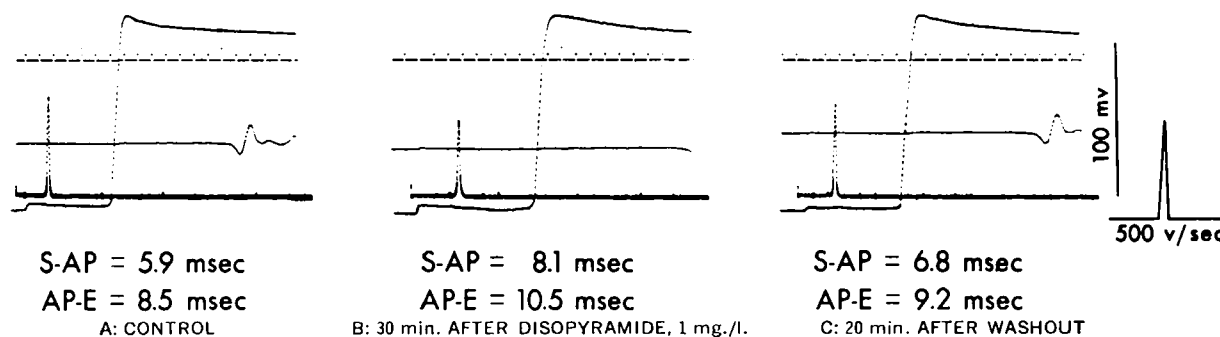

S-AP = 5.9 msec
AP-E = 8.5 msec
A: CONTROL

S-AP = 8.1 msec
AP-E = 10.5 msec
B: 30 min. AFTER DISOPYRAMIDE, 1 mg./l.

S-AP = 6.8 msec
AP-E = 9.2 msec
C: 20 min. AFTER WASHOUT

500 v/sec

Figure 5—*Effects of 1 mg./l. disopyramide on resting potential, maximum rate of depolarization* (dV/dt *max*), *and conduction velocity in a canine Purkinje fiber-papillary muscle preparation. A is the control. The top tracing is the zero reference line with time marks of 1 and 10 msec. The second tracing shows the surface electrogram* (E) *recorded from the distal end of the specialized ventricular conduction system. The third tracing shows the* dV/dt *max of the action potential, and the bottom tracing shows the action potential* (AP) *recorded from a Purkinje fiber in the proximal end of the same strand of specialized ventricular conduction system. Stimulus artifact* (S) *can be seen at the beginning of the third and the fourth tracings. B shows that 1 mg./l. disopyramide decreased the maximum rate of rise of the action potential and conduction velocity, without affecting either the resting potential or the overshoot. These effects of disopyramide are largely reversible, and C shows the improvement of* dV/dt *max and conduction velocity after washout. Calibrations for voltage and* dV/dt *are indicated on the right side of the figure.*

A: CONTROL

B: 5 min. AFTER DISOPYRAMIDE, 1 mg./l.

C: 15 min. AFTER DISOPYRAMIDE, 1 mg./l.
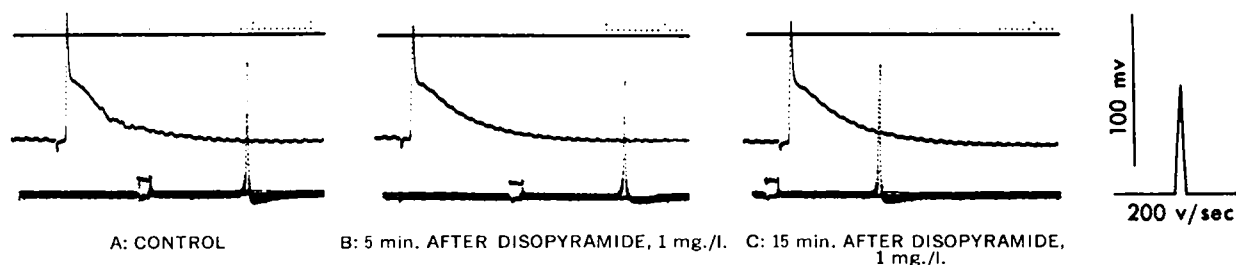
200 v/sec

Figure 6—*Effects of disopyramide on the action potential of a human atrial muscle fiber. A is the control. The top tracing is the zero reference line showing time marks of 10 and 100 msec. The square pulse on the bottom tracing shows the stimulus intensity* (10% *above threshold), and the maximum rate of depolarization* (dV/dt *max) is also registered. Note that 1 mg./l. disopyramide caused a slight and transient depolarization, associated with a decrease in* dV/dt *max and overshoot* (B). *The atrial cell recovered quickly despite the continued presence of disopyramide in the perfusate* (C).
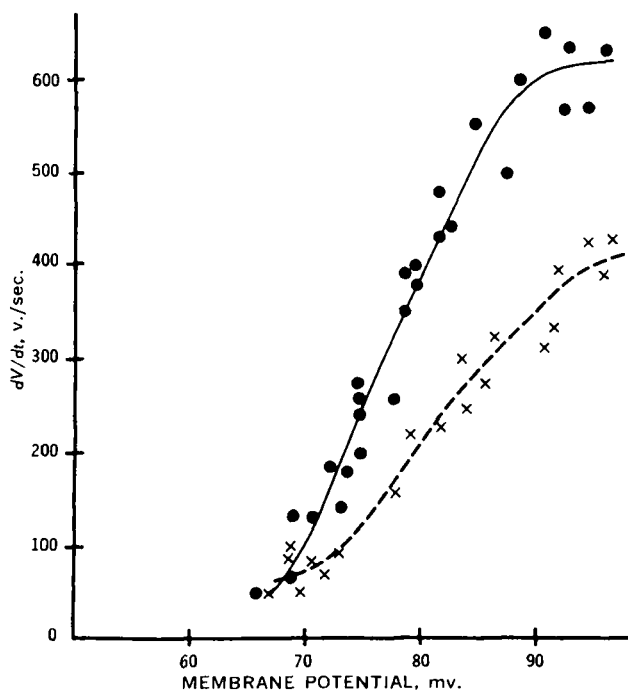
Figure 7—*Effects of disopyramide on membrane responsiveness in dog Purkinje fibers. The control curve is one characteristic of a normal Purkinje fiber, with the maximum rate of rise* (dV/dt) *of about 600 v./sec. It is evident that 2 mg./l. disopyramide caused a shift of the membrane responsiveness curve to the right, and there was also depression of* dV/dt *to around 400 v./sec., while the maximum resting potential remained unchanged (90-95 mv.). The measurements were made 45 min. after exposure to disopyramide. Key:* ●—●, *control; and* ×- - -×, *after 2 mg./l. disopyramide.*

tively speaking, the dog Purkinje fibers used in the present study are perhaps at least 5 times more sensitive to the depressant effect of disopyramide than the rabbit atrial muscle fibers. This is consistent with our own data showing that human atrial muscle fibers are more resistant to disopyramide than dog Purkinje fibers. These differences in sensitivity to disopyramide, if not due to species difference, could be explained by the well-known fact that the specialized ventricular conduction system is more sensitive to drugs than ordinary cardiac muscle fibers.

Like quinidine, disopyramide also depresses myocardial contractility and left ventricular function. It would be an undesirable property if the depressant effect of disopyramide on myocardial performance, which outlasts its electrophysiological effects in the dog heart, is also found in man.

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Pharmacokinetics of Iodochlorhydroxyquin in Man

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Abstract ☐ A method of extracting iodochlorhydroxyquin from plasma and quantitating by GLC was developed and used to study the pharmacokinetics in man. A clearcut dose–plasma concentration relationship was obtained, and no evidence of accumulation was found.

Keyphrases ☐ Iodochlorhydroxyquin --pharmacokinetics in man, dose-plasma concentration relationships, GLC determination ☐ Quinolines (iodochlorhydroxyquin)—GLC analysis of human plasma samples, pharmacokinetics ☐ Pharmacokinetics--iodochlorhydroxyquin half-life, dose–plasma concentration relationships, GLC determination ☐ GLC—analysis of iodochlorhydroxyquin in human plasma samples

Recently two publications (1, 2) appeared dealing with the GLC of halogenated quinolines using flame-ionization detection. Neither publication was concerned with the analysis of extracts derived from biological material.

To study the pharmacokinetics of iodochlorhydroxyquin, 5-chloro-7-iodo-8-hydroxyquinoline, a sensitive and specific method of analysis was needed; the presence of two halogen atoms in the molecule made GLC using an electron-capture detector an obvious choice. Acetylation at the 8-position of the quinoline ring system provided a derivative of sufficient volatility to allow 50-ng./ml. concentrations to be measured.

EXPERIMENTAL

By using the developed method, the kinetics in man were studied as follows.

Single-Dose Administration—Six volunteers were given single oral doses of 250 and 1500 mg. of iodochlorhydroxyquin powder[1]

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[1] Iodochlorhydroxyquin was administered as a powder with the addition of 7% N-stearoyl-N',N'-diethylethylenediamine (Sapamine). This formulation is available commercially as Entero-Vioform.