Effects of disopyramide on electrophysiological properties of specialized conduction system in man and on accessory atrioventricular pathway in Wolff-Parkinson-White syndrome

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Seven patients with normal specialized conduction system and three patients with the Wolff-Parkinson-White (WPW) syndrome were studied using programmed stimulation of the heart before and after the administration of intravenous disopyramide. The principal effect of this drug was to prolong the effective refractory period of the atria and ventricles, and to prolong the effective refractory period of the anomalous pathway in the WPW syndrome. In addition, it prolonged the conduction time in the anomalous pathway in the WPW syndrome. These findings suggest that disopyramide would be a useful and safe drug in the management of certain atrial and ventricular arrhythmias and in the management of the Wolff-Parkinson-White syndrome with atrial fibrillation.

Disopyramide (Rythmodan) is an antiarrhythmic agent which has been found valuable in the management of extrasystoles and tachycardias of both supraventricular and ventricular origin (Vismara, Mason, and Amsterdam, 1974; Katz *et al.*, 1963; Desruelles *et al.*, 1967). Using techniques of intracardiac recordings and programmed electrical stimulation of the heart, we have studied the effects of disopyramide on the electrophysiological properties of the specialized conduction system in man, and in addition its effect on the anomalous atrioventricular pathway in the Wolff-Parkinson-White (WPW) syndrome.

Patients and methods

Ten patients, 5 male and 5 female, were studied and their clinical details are shown on Table 1. Case 1 underwent an electrophysiological study while undergoing routine cardiac catheterization for a ventricular septal defect. Cases 2, 4, 5, and 6 were undergoing routine electrophysiological study for the investigation of recurrent rapid palpitations. In each patient the resting electrocardiogram was normal and no tachycardia could be initiated during the study which in each patient demonstrated a normal conduction system. Cases 3 and 7 underwent electrophysiological study for the further investigation of previously documented ventricular

tachycardia: in both patients the resting electrocardiograms were normal. Cases 8, 9, and 10 had the WPW syndrome with recurrent bouts of supraventricular tachycardia; the resting electrocardiogram in each patient showed the typical features of the WPW syndrome. Informed consent was obtained from each patient or from the parents of Cases 1, 8, and 9. All patients underwent the electrophysiological study in the postabsorptive non-sedated state. No patient was receiving drug medication at the time of the study. Three bipolar electrode catheters were introduced percutaneously via one or both femoral veins. One catheter was positioned high in the right atrium to record a high right atrial electrogram. One catheter was positioned across the tricuspid valve to record a His bundle electrogram using the technique described by Scherlag *et al.* (1969). The His bundle electrogram was recorded at a filter setting of 40 to 50 c/s. The intracardiac recordings were made simultaneously with leads I, III, V₁, and V₆ of the surface electrocardiogram. All recordings were made on an 8-channel Elema Mingograph 81 at a paper speed of 100 mm/s. The third catheter was positioned in either the right atrium or ventricle for atrial or ventricular pacing and inducing single or double atrial or ventricular premature beats. In Cases 8 and 10 an additional catheter electrode was positioned in the coronary sinus to record left atrial activity.

A Devices 4270¹ stimulator was used for atrial and

¹Devices Instruments Ltd., Welwyn Garden City, Hertfordshire.

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TABLE I Clinical details

Case No.	Age	Sex	Clinical diagnosis
1	17	M	VSD
2	30	F	Paroxysmal tachycardia
3	30	F	Paroxysmal ventricular tachycardia
4	49	F	Paroxysmal tachycardia
5	40	F	Paroxysmal tachycardia
6	33	M	Paroxysmal tachycardia
7	32	M	Paroxysmal ventricular tachycardia
8	15	F	Type A WPW syndrome
9	11	M	Type B WPW syndrome
10	34	M	Type A WPW syndrome

ventricular pacing. The heart was driven at a constant frequency to avoid changes in excitability or refractoriness caused by variations in rate or rhythm. Single or double atrial or ventricular premature beats were delivered at a preset time in the cardiac cycle, after every eighth beat of the basic driven rhythm.

The following measurements were made.

St_1-St_2 : time in milliseconds between two successive pacing stimuli.

$HRA-LRA$: time in milliseconds from the high right atrial potential as recorded by the electrode catheter high in the right atrium to the low right atrial potential as seen on the His bundle electrogram. The atrial pacing electrode was usually positioned at the superior vena cava-right atrial junction in order to stimulate the atria in the region of the sinoatrial node.

$LRA-H$: time in milliseconds from the atrial potential on the His bundle electrogram to the His potential on the His bundle electrogram. This measurement represents atrioventricular nodal conduction.

$H-V$: time in milliseconds from the His potential to the earliest onset of ventricular activation as seen on the surface electrogram leads.

$St-d$: time in milliseconds from the pacing stimulus artefact to the onset of the delta wave on the surface electrocardiogram in the patients with the WPW syndrome.

$V-A'$: retrograde conduction time in milliseconds in the anomalous pathway during reciprocal tachycardia from the onset of ventricular activation on the surface electrocardiogram to the earliest onset of atrial activation as seen on the right atrial electrogram (HRAE) in Case 9 (Type B WPW) and the earliest onset of atrial activation as seen on the coronary sinus electrogram in Cases 8 and 10 (Type A WPW).

$A'-V$: antegrade conduction time in milliseconds in the atrioventricular node His pathway during reciprocal tachycardia measured from the earliest onset of atrial activation as recorded either on the right atrial electrogram (Case 9) or coronary sinus electrogram (Cases 8 and 10).

$R-R$: cycle length of the tachycardia in milliseconds.

ERP_{atr} : effective refractory period of atrium is the longest St_1-St_2 interval that does not result in atrial depolarization by St_2 .

FRP_{AVN} : the functional refractory period of the atrioventricular node is the shortest H_1H_2 interval resulting from two conducted atrial depolarizations.

ERP_{AVN} : the effective refractory period of the atrioventricular node is the longest LRA_1-LRA_2 interval that does not result in conduction of LRA_2 to the His bundle.

$ERP_{ventricle}$: effective refractory period of the ventricle is the longest St_1-St_2 interval during ventricular premature stimulation at which St_2 fails to produce a ventricular depolarization.

$ERP_{anomalous\ bypass}$ (antegrade or retrograde): antegrade or retrograde effective refractory period of the anomalous bypass is the longest atrial or ventricular premature beat interval at which the anomalous pathway failed to conduct either antegradely or retrogradely. The criteria for conduction occurring retrogradely in an anomalous bypass have been described previously by Wellens and Durrer (1974).

Latency time is the time from the pacing stimulus artefact to the earliest onset of atrial or ventricular activation. All measurements were made in milliseconds.

The above measurements were made before the administration of disopyramide and were repeated at 2, 5, 10, 15, 20, and 30 minutes after the intravenous administration of disopyramide in a dose of 2 mg/kg body weight. In the patients with the WPW syndrome the tachycardia was initiated before the administration of the drug in each case in order to study the effect of the drug on the reciprocal circuit during tachycardia.

Only the maximal changes in the conduction times or refractory periods after disopyramide administration are reported in the Tables and in each patient this occurred between 2 and 5 minutes after administration. In most patients all the measurements had returned to near control values after 30 minutes.

The conduction times before and after disopyramide are given at the same basic St_1-St_2 intervals to avoid changes in conduction caused by changes in cycle length. For the same reason refractory periods were recorded before and after disopyramide using the same basic cycle during premature stimulation.

Results

No patient suffered any side effect from the administration of disopyramide.

Patients with normal conduction system

Table 2 summarizes the effects of this drug on intra-atrial conduction ($HRA-LRA$), atrioventricular nodal conduction ($LRA-H$), and His Purkinje conduction ($H-V$) in Cases 1 to 7. In 4 patients the $HRA-LRA$ interval increased by 10 ms suggesting an increase in atrial conduction time. Small changes in $LRA-H$ time were noted. In 5 patients, the conduction time increased from between 5 and 15 ms, in one patient there was a 10 ms

TABLE 2 *Intra-atrial, atrioventricular nodal, and intraventricular conduction times (ms) before and after disopyramide*

Case No.	HRA-LRA		LRA-H		H-V		St ₁ -St ₂	
	Before	After	Before	After	Before	After	Before	After
1	50	60	60	70	50	50	570	570
2	50	60	120	135	35	35	570	570
3	30	30	60	70	35	55	600	600
4	60	60	100	100	35	40	600	600
5	60	70	60	70	35	35	600	600
6	50	50	120	110	50	50	600	600
7	60	70	125	130	50	55	600	600

TABLE 3 *Atrial, atrioventricular nodal, and ventricular refractory periods (ms) before and after disopyramide*

Case No.	ERP atr		FRP AVN		ERP AVN		ERP ventricle	
	Before	After	Before	After	Before	After	Before	After
1	230	270	400	400	< 230	< 270	170	190
2	210	280	450	450	270	290	220	230
3	250	365	450	450	280	< 365	320	370
4	270	290	560	550	320	320	200	230
5	240	290	450	450	260	< 290	210	230
6	190	270	430	450	300	300	170	185
7	235	270	460	460	345	350	240	255

decrease, and in one patient there was no change. Intraventricular conduction (H-V) was unchanged in 4 patients, increased by only 5 ms in 2 patients, and increased by 20 ms in 1 patient; this latter patient (Case 3) had a normal H-V time before disopyramide administration.

Table 3 summarizes the results of the measurements of the refractory periods in Cases 1 to 7. The effective refractory period of the atria was increased in each patient by between 20 and 115 ms.

The functional refractory period of the atrioventricular node was minimally changed in 2 patients only.

The effective refractory period of the atrioventricular node could not be measured either before or after disopyramide in Case 1 owing to the effective refractory period of the atria being longer than that of the atrioventricular node. In Cases 3 and 5 the effective refractory period of the atrium was increased by disopyramide to such an extent that it became longer than that of the atrioventricular node and as such the effective refractory period of the atrioventricular node could not be measured in these 2 patients after disopyramide administration. In the remaining patients the effective refractory period of the atrioventricular node was only minimally affected in that it increased by 5 ms in one

patient, by 20 ms in another, and was unchanged in 2 patients.

The effective refractory period of the ventricle was consistently increased by between 10 and 50 ms in all 7 patients after the administration of disopyramide.

During refractory period measurements it was found that after disopyramide administration the latency time increased in some patients, particularly during premature stimulation.

Patients with WPW syndrome

Table 4 summarizes the effects of disopyramide on the antegrade conduction time in the accessory pathway as represented by the St-d interval, in the

TABLE 4 *Antegrade conduction times (ms) in the accessory pathway in WPW syndrome before and after disopyramide*

Case No.	St-d		St ₁ -St ₂
	Before	After	
8	145	210	600
9	120	Bypass blocked	600
10	70	110	600

TABLE 5 Antegrade and retrograde effective refractory period (ms) of the accessory pathway before and after disopyramide

Case No.	ERP anomalous bypass antegrade		ERP anomalous bypass retrograde	
	Before	After	Before	After
8	350	400	290	330
9	290	Bypass blocked	280	Bypass blocked
10	285	350	270	310

TABLE 6 Antegrade and retrograde conduction times (ms) during supra-ventricular tachycardia before and after disopyramide

Case No.	V-A'		A'-V		R-R	
	Before	After	Before	After	Before	After
8	130	170	165	190	295	360
9	120	170	180	130	300	300
10	170	215	230	135	400	350

FIG. Recording obtained from Case 9 during tachycardia (left-hand panel) and after disopyramide administration (right-hand panel). In the right-hand panel the first three beats are the last three of the tachycardia and the fourth beat is the first beat of sinus rhythm. HRAE=high right atrial electrogram; I, III, V1, and V6=surface electrocardiogram leads; AV=atrio-ventricular region; A'=retrograde atrial potential as seen on the HRAE; K=Kent accessory pathway; H=atrioventricular node His pathway; V-A'(HRA)=retrograde conduction time (ms) from the onset of ventricular activation as seen on the surface electrocardiogram to the retrograde atrial potential as seen on the HRAE; A'(HRA)-V=antegrade conduction time (ms) from the retrograde atrial potential as seen on the HRAE to the onset of ventricular activation as seen on the surface electrocardiogram.

3 patients with the WPW syndrome. It can be seen that the conduction time increased from between 40 and 65 ms in Cases 8 and 10 and in Case 9 antegrade conduction in the accessory pathway was totally blocked and did not return until 40 minutes after disopyramide administration.

Table 5 summarizes the effects of disopyramide on the effective refractory periods of the accessory pathway for both antegrade and retrograde conduction. In Case 9 the accessory pathway was totally blocked both antegradely and retrogradely and so the refractory period could not be measured. In Cases 8 and 10 the effective refractory period of the anomalous pathway for antegrade conduction increased by 50 ms and 65 ms, respectively, and for retrograde conduction by 40 ms in both patients.

Table 6 summarizes the effect of disopyramide on retrograde conduction and antegrade conduction during reciprocal tachycardia. After disopyramide the retrograde conduction time in the anomalous bypass was prolonged in Cases 8, 9, and 10 by 40, 50, and 45 ms, respectively. The antegrade conduction time in the atrioventricular node His pathway was prolonged in Case 8 by 25 ms but shortened in Cases 9 and 10 by 50 ms and 95 ms, respectively. The net result was to lengthen the cycle length of the tachycardia in Case 8, the cycle length of the tachycardia shortened by 50 ms after disopyramide in Case 10, and the cycle length was unchanged in Case 9 (see Fig. which shows the termination of a supraventricular tachycardia in Case 9 after disopyramide administration). After the administration of disopyramide the tachycardia was terminated after 2 minutes and 2½ minutes, respectively, in Cases 9 and 10 and the antegrade and retrograde conduction times were measured during the last cycle of the tachycardia before termination. In Case 8 the tachycardia was not terminated by disopyramide and the antegrade and retrograde conduction times were measured two minutes after the administration of disopyramide, at which time maximum prolongation of the retrograde conduction time had occurred. In Case 8 the tachycardia was finally terminated by an appropriately timed right ventricular premature beat.

Discussion

Disopyramide is an antiarrhythmic agent with an antiarrhythmic spectrum similar to that of quinidine. In the electrophysiological study presented in this paper the conduction times in the atria, atrioventricular node, and His Purkinje system show only small changes except in one patient who had a 20 ms increase in intraventricular conduction time. Quinidine therefore differs in that it is known to

depress His Purkinje conduction (Damato and Lau, 1970).

The refractory period measurements in Cases 1 to 7 showed that the main effect of disopyramide was to increase the effective refractory period of the atria, in one patient by as much as 115 ms. Similar results were also obtained by Josephson *et al.* (1973), though the prolongation of atrial refractory period in their cases was not so striking.

In this study a consistent prolongation of the effective refractory period of the ventricle was found but was not so obvious as the prolongation of atrial refractory period.

The effect of disopyramide on the effective refractory period of the atrioventricular node was small and could not be measured in 3 patients as the effective refractory period of the atria was prolonged in excess of that of the atrioventricular node.

This predominant effect of disopyramide on the atria and ventricles may explain its apparent effectiveness in the treatment of atrial and ventricular extrasystoles (Vismara *et al.*, 1974; Katz *et al.*, 1963; Desruelles *et al.*, 1967). Supraventricular tachycardias which are caused by a re-entry or reciprocal mechanism within the atria or within the atrioventricular node may be initiated by atrial extrasystoles; the effect of disopyramide on the atria and its reported effectiveness in the suppression of atrial extrasystoles should, therefore, make this a valuable drug in the prevention of paroxysms of supraventricular tachycardia caused by the above two mechanisms. In terms of termination rather than prevention of a supraventricular tachycardia, if the tachycardia is caused by a re-entry mechanism within the atria the prolongation of the effective refractory period of the atria by disopyramide should make this a useful drug for the termination of such tachycardias. However, because of disopyramide's minimal effect upon the atrioventricular node it would not be expected to be so effective in terminating a supraventricular tachycardia caused by an intra-atrioventricular nodal reciprocal mechanism.

The prolongation of atrial effective refractory period by disopyramide may well explain the mechanism by which this drug is reported to reduce the incidence of recurrence of atrial fibrillation after successful electroconversion to sinus rhythm (Härtel, Louhija, and Kontinen, 1974).

The prolongation of the effective refractory period of the ventricles may explain why disopyramide is effective in the suppression of ventricular ectopics. It is now well recognized that ventricular tachycardia in some patients may well be caused by a re-entry or reciprocal mechanism (Wellens, Schuilenburg, and Durrer, 1972; Spurrell, Sowton, and

Deuchar, 1973). The site of the re-entry mechanism in these patients is uncertain; it may be in the main bundle-branches, the distal His Purkinje tissue, ordinary ventricular myocardium, or combinations of these three. In this paper it has been shown that disopyramide prolongs the effective refractory period of the ventricle, and Josephson *et al.* (1973) have shown that disopyramide prolongs the effective refractory period of the His Purkinje system: it would, therefore, be reasonable to expect disopyramide to be of value in the termination of re-entry ventricular tachycardia when the re-entry circuit is in one of the above sites.

Two main types of tachycardia occur in the WPW syndrome. Firstly, there is the circus movement supraventricular tachycardia which involves antegrade conduction by way of the atrioventricular node His pathway and retrograde conduction by way of the accessory pathway. Any therapeutic agent which is able to block one part of the reciprocal circuit may be useful in terminating tachycardias of this sort. Drugs which act predominantly on the atrioventricular node such as digoxin or verapamil (Roy, Spurrell, and Sowton, 1974) are useful drugs for their blocking action on the antegrade pathway of the tachycardia. In this study disopyramide has been shown to delay conduction and prolong the effective refractory period of the anomalous bypass in the WPW syndrome and so should be of value in the termination of the circus movement tachycardia, and indeed the tachycardia was terminated in Cases 9 and 10 (Fig.). In these two patients the retrograde conduction time in the accessory pathway lengthened after disopyramide but the antegrade conduction time in the atrioventricular node His pathway shortened. In Case 10 this shortening of antegrade conduction time was in fact sufficient to increase the rate of the tachycardia (the cycle length was reduced from 400 to 350 ms). The reason for this shortening of antegrade conduction is not known as the studies in Cases 1 to 7 did not suggest such an effect on the atrioventricular node His pathway. It may be that during reciprocal tachycardia the prolongation of conduction time in the retrograde part of the circuit was sufficient to allow longer for the atrioventricular nodal His pathway to recover and result in a faster atrioventricular nodal conduction time. In Case 8, however, disopyramide prolonged both retrograde and antegrade conduction times and it can only be assumed that this must have resulted from a direct effect by the drug on the atrioventricular node (the H-V time was unchanged). This finding is a little bizarre as in Cases 1 to 7 no such prolongation of atrioventricular nodal conduction by disopyramide was observed. The tachycardia was not terminated

by the drug in Case 8 and this may be because disopyramide had prolonged the conduction times in both parts of the re-entry circuit, thereby allowing a balance of conduction time and refractoriness to remain between antegrade conduction in the atrioventricular node His pathway and retrograde conduction in the anomalous pathway such that the tachycardia could continue but with a longer cycle length.

The other type of tachycardia associated with the WPW syndrome is atrial fibrillation or atrial flutter. In the absence of an anomalous pathway the ventricles are protected from rapid activation during atrial fibrillation by the development of physiological block within the atrioventricular node. However, in the WPW syndrome ventricular activation may occur by way of the anomalous bypass and the frequency will depend upon the effective refractory period of the anomalous bypass. If the refractory period of the accessory pathway is too short, then there is a risk of ventricular fibrillation caused by activation of the ventricles at high frequency via the anomalous pathway from the fibrillating atria. Therefore, any drug that shortens the refractory period of the anomalous pathway will increase the risk of ventricular fibrillation when the refractory period of the bypass tract is already short. This situation has been described by Dreifus *et al.* (1971) in a patient with the WPW syndrome and atrial fibrillation, in whom recurrent bouts of ventricular fibrillation appeared to be related to the administration of digoxin. There is evidence that in some cases of the WPW syndrome digoxin shortens the refractory period of the anomalous pathway (Wellens and Durrer, 1973) and this could explain the above phenomenon. It is, therefore, important to assess the electrophysiological properties of a drug whose use is going to be considered in the WPW syndrome. In this paper disopyramide has been shown to prolong the effective refractory period of the anomalous bypass and so should be a safe and useful drug to administer to patients with the WPW syndrome and atrial fibrillation. In this context, therefore, administration of disopyramide would be expected to reduce the ventricular rate during atrial fibrillation.

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