THE EFFECT OF INTRAVENOUS DISOPYRAMIDE PHOSPHATE ON RECURRENT PAROXYSMAL TACHYCARDIAS

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- 1 Recurrent paroxysmal atrial, atrioventricular and ventricular tachycardias in 50 patients without acute coronary insufficiency, heart failure or metabolic abnormality were treated with disopyramide phosphate in a dose of 2 mg/kg body weight infused over 5 min.
- 2 Conversion to sinus rhythm within 10 min of the completed infusion occurred in 10 of 14 (71%) patients with paroxysmal 'lone' atrial fibrillation, 3 of 7 (43%) patients with paroxysmal atrial flutter, 6 of 9 (67%) patients with paroxysmal atrial tachycardia, 5 of 9 (56%) patients with paroxysmal atrioventricular tachycardia associated with the Wolff-Parkinson-White syndrome and 8 of 11 (73%) patients with paroxysmal ventricular tachycardia.
- 3 Side effects: significant systemic hypotension in 3, high grade AV block in 1, an increased ventricular response producing symptoms in 4, post conversion asystole in 1 and sinus bradycardia in 2.
- 4 The anti-arrhythmic effect and arrhythmogenic side effects may be related to both the direct membrane stabilizing effect and the anticholinergic effect of disopyramide.

Introduction

Disopyramide phosphate is a butyramide derivative, structurally dissimilar to other antiarrhythmic drugs, which possesses the combined electrophysiological characteristics of a membrane stabilizing or local anaesthetic (Sekiya & Vaughan-Williams, 1963) and anticholinergic (Baines, Davies, Kellett & Munt, 1976; Birkhead & Vaughan-Williams, 1977) agent. Although the intravenous formulation of disopyramide has been established as variably successful in the treatment of paroxysmal arrhythmias, previous reports have not clearly distinguished between tachycardias occurring during acute myocardial infarction and those occurring in the absence of an acute coronary insult. It is also difficult to discern whether or not the arrhythmias are associated with cardiac failure or metabolic abnormalities and if they are recurrent, acute or chronic. Many of these so-called paroxysmal arrhythmias included in these studies have comprised of a variety of atrial or ventricular extrasystoles. Here we report the effects of intravenous disopyramide on paroxysmal sustained atrial, atrioventricular or ventricular tachycardias which occurred in patients without acute coronary insufficiency, heart failure or metabolic aberration. The antiarrhythmic effects and arrhythmic side effects encountered in this group of patients are discussed in terms of the contribution of the direct and anticholinergic effects of the drug.

Methods

This study includes 50 patients with recurrent paroxysmal tachycardias diagnosed from the surface ECG or confirmed by intracardiac electrography and programmed stimulation studies (Wellens, 1971). Most of the tachycardias submitted to treatment occurred spontaneously. Each tachycardia was observed for 5 min or longer to ensure that it was stable. The blood pressure was recorded by a sphygmomanometer prior to treatment, during the infusion of disopyramide and 5 min after the infusion was completed. Disopyramide phosphate in a dose of 2 mg/kg body weight was infused over a 5 min period.

The ECG was recorded at one minute intervals and the termination of the tachycardia was retrieved directly from a continuous paper recording or from an electromagnetic tape recording loop. The arrhythmias associated with Wolff-Parkinson-White syndrome were systematically studied in the catheterization laboratory. These tachyarrhythmias were stimulated electrically and recordings were made on an Elema Mingograf multichannel recorder at paper speeds of 25 or 100 mm/s. Biopolar intracardiac electrograms were filtered to between 50 and 700 Hz and recorded simultaneously with 3 or 4 surface leads.

None of the patients included in this study was suffering from acute coronary distress and none had clinical or radiographic evidence of cardiac failure or

Figure 1 Surface electrocardiogram illustrating the typical response of paroxysmal 'lone' atrial fibrillation to intravenous disopyramide. The pretreatment (a) strip shows atrial fibrillation with fine fibrillatory waves and a controlled ventricular response. During the infusion of disopyramide (b) the baseline oscillations coarsen, increase in amplitude and take on the appearance of flutter/fibrillation. The ventricular rate increases. Three minutes after the completed infusion (c) the atrial arrhythmia gives way to normal sinus rhythm.

cardiogenic shock. Thyroid function tests and other biochemical and haematological tests were normal. The patients had not received any cardioactive medication for at least three days prior to the study. Thirty-one patients were males (aged 24–73 years) and 19 females (aged 29–64 years). The arrhythmias studied were:

- (1) paroxysmal 'lone' atrial fibrillation—14 patients
- (2) paroxysmal atrial flutter—7 patients
- (3) paroxysmal atrial tachycardia—9 patients
- (4) paroxysmal orthodromic Wolff-Parkinson-White atrioventricular tachycardia—9 patients
- (5) paroxysmal ventricular tachycardia—11 patients

Results

Paroxysmal atrial fibrillation (Figure 1)

Of 14 patients with paroxysmal 'lone' atrial fibrillation, 10 converted to sinus rhythm within 10 min of completion of the disopyramide infusion. Immediately following the cessation of atrial fibrillation normal sinus rhythm was present in five patients but in the remainder a variety of atrial, junctional or ventricular escape mechanisms dominated the cardiac rhythm. Ventricular asystole requiring resuscitation measures did not occur in this group but the sinus rate was 55 beats/min and 59

Figure 2 Simultaneous surface and intracardiac recordings (HRAE = high right atrial electrogram; CSE = coronary sinus electrogram; RVAE = right ventricular apical electrogram; I, AVF V1 and V6 = surface electrocardiograms) of paroxysmal atrial fibrillation associated with Wolff-Parkinson-White syndrome, Type A, due to an anomalous left atrial—left ventricular connexion. In the left panel fine, variable electrograms are seen in both the left (CSE) and right (HRAE) atrial tracings. The ventricular response is rapid and the QRS complexes are pre-excited. Two minutes after the infusion of disopyramide phosphate the left atrial deflections are regular and rapid (left atrial flutter) whereas the right atrium continues to fibrillate. The ventricular response slows and becomes regular (2 : 1 conducted left atrial flutter). Six minutes following the infusion pre-excitation is abolished.

beats/min in two patients. In one case high grade A-V block occurred and persisted for 1 h following disopyramide infusion. The resultant ventricular escape rate in this case did not fall below 45 beats/minute.

The infusion of disopyramide phosphate usually resulted in 'coarsening' of the fibrillatory activity and in two patients produced typical atrial flutter prior to conversion to sinus rhythm. In 11 of the 14 patients treated, the ventricular response during atrial fibrillation increased by 10–50 beats/min following the infusion. In two patients with spontaneous atrial fibrillation associated with the Wolff-Parkinson-White syndrome, treatment with intravenous disopyramide resulted in considerable slowing of the ventricular response and increase in the minimum R-R interval between successive preexcited QRS complexes. In one of these patients ventricular preexcitation was temporarily abolished (Figure 2). In neither case did atrial fibrillation revert to sinus rhythm.

Figure 3 Surface electrocardiogram illustrating a response to atrial flutter with 2 : 1 A-V conduction (a) (atrial rate 300 beats/min; ventricular rate 150 beats/min). Three minutes following disopyramide 150 mg i.v. (b) the flutter frequency had slowed from 300 beats/min to 240 beats/min and intermittent 1 : 1 A-V conduction is seen. Two minutes later (c) the flutter frequency was reduced to 225 beats/min and uninterrupted 1 : 1 A-V conduction occurred, resulting in a ventricular rate of 225 beats/min.

Paroxysmal atrial flutter

Seven patients with paroxysmal atrial flutter (two associated with the Wolff-Parkinson-White syndrome) were treated with intravenous disopyramide. Three patients reverted to sinus rhythm. In all cases the flutter frequency was markedly reduced (305 ± 15 to 235 ± 40 beats/min) and in four examples the A-V conduction ratio decreased leading to a net increase in the ventricular rate (Figure 3). In three patients this faster ventricular rate necessitated additional treatment by A-V nodal blockade with verapamil to control ventricular rate. In the two examples of atrial flutter associated with the Wolff-Parkinson-White

syndrome, the A-V conduction ratio was 1 : 1 at the onset with both atrial and ventricular rates of 279 and 290 beats/min. Intravenous disopyramide resulted in marked slowing of the atrio-ventricular rate, in one patient, to 194 beats/min (Figure 4), and in the other to 230 beats/minute.

Paroxysmal atrial tachycardia

The medical conversion of nine examples (four with A-V conduction block) of atrial tachycardia was attempted. Six of these (two patients with a 2 : 1 A-V conduction ratio) reverted to sinus rhythm. In the remainder the tachycardia cycle length was increased in two patients A-V conduction block was relieved resulting in a higher ventricular rate (Figure 5).

Paroxysmal WPW (atrioventricular) re-entrant tachycardia

Nine patients with paroxysmal circus movement atrioventricular tachycardia involving a direct A-V anomalous connexion, were treated with intravenous disopyramide. In four patients the tachycardia cycle length increased because of delay in the ventriculo-atrial limb, but the tachycardia was not terminated. In five other patients the tachycardia gave way to sinus rhythm following ventriculo-atrial block. In three of these cases the cycle length increased, in one it remained unchanged, but in one patient the tachycardia accelerated prior to termination in the ventriculo-atrial direction (Figure 6). This patient also developed gross right-bundle branch delay during tachycardia, which persisted following termination. In one patient, termination of tachycardia was followed by a 6 s period of ventricular asystole before a transient period of chaotic atrial escape and finally sinus rhythm occurred.

In all patients in this group the A-V nodal conduction time (A-H interval) decreased and the presence or absence of changes in the ventriculo-atrial conduction time determined the ultimate cycle length.

Table 1 Conversion of paroxysmal arrhythmias following intravenous disopyramide phosphate (2 mg/kg over 5 min).

Arrhythmia	Total	Success		Failure	
			%		%
Paroxysmal atrial fibrillation	14	10	71	4	29
Paroxysmal atrial flutter	7	3	43	4	57
Paroxysmal atrial tachycardia	9	6	67	3	33
Paroxysmal Wolff-Parkinson-White tachycardia	9	5	56	4	44
Paroxysmal ventricular tachycardia	11	8	73	3	27

Figure 4 Surface and intracardiac recordings (DCSE = distal coronary sinus electrogram; PCSE = proximal coronary sinus electrogram; LRAE = low right atrial electrogram; HBE = His bundle electrogram) of atrial flutter with 1 : 1 AV conduction via an anomalous atrioventricular connection. Prior to disopyramide the atrial and ventricular cycle length is 215 ms (279 beats/min) and the ventricular QRS complexes demonstrate Type A pre-excitation. Four minutes after the infusion of disopyramide the flutter cycle length increased to 310 ms (194 beat/min).

Table 2 Arrhythmic and hypotensive side effects encountered following intravenous disopyramide phosphate (2 mg/kg over 5 min)

Patient	Arrhythmia	Side effects	
		ECG	BP
CT	PAF	1° + 2° AV block	—
AP	PAF	Sinus bradycardia	—
RS	PAF	Sinus bradycardia	—
BL	PAFI	↑ Ventricular rate	hypotension
CR	PAFI	↑ Ventricular rate	—
DT	PAFI	—	hypotension
FS	PAT	↑ Ventricular rate	—
AT	PAT	↑ Ventricular rate	hypotension
ER	PAVRT	6 s asystole	—

PAF = paroxysmal atrial fibrillation

PAFI = paroxysmal atrial flutter

PAT = paroxysmal atrial tachycardia

PAVRT = paroxysmal atrioventricular tachycardia

Figure 5 Surface electrocardiogram of paroxysmal atrial tachycardia with block (2:1 AV conduction). Prior to treatment (a) the atrial rate is 196 beats/min. Two minutes after the completed infusion of 150 mg disopyramide (b) the atrial rate had slowed to 145 beats/min and AV block was relieved. The ventricular rate, therefore, increased from 98 beats/min to 145 beats/min before the atrial tachycardia was extinguished giving way to normal sinus rhythm.

Paroxysmal ventricular tachycardia

In eleven cases of recurrent paroxysmal ventricular tachycardia in patients without acute coronary disease a temporary pacing catheter was inserted into

Figure 6 Surface and intracardiac tracings of paroxysmal atrio-ventricular tachycardia associated with the Wolff-Parkinson-White syndrome. Prior to disopyramide (a) the tachycardia cycle length is 305 ms (197 beats/min) and the QRS complexes show incomplete right bundle branch block. Following treatment with disopyramide 150 mg i.v. (b) the tachycardia cycle length decreases to 255 ms (235 beats/min) by shortening of the AV nodal conduction time (His bundle deflection is indicated by an arrow) and right bundle branch delay is more pronounced. The tachycardia terminates by the development of block in the anomalous connexion (no atrial signal following the last QRS complex of the tachycardia) and is followed by sinus rhythm with right bundle branch delay. CL, cycle length.

the right ventricle. Seven of these tachycardias could be terminated by overdrive ventricular pacing at rates between 10 and 50 beats/min faster than the tachycardia rate. These tachycardias were re-stimulated and intravenous disopyramide given to all eleven patients. Within 10 min eight tachycardias had terminated (Figure 7) and the three remaining cases could be terminated by overdrive ventricular pacing. In two of those, the tachycardias were refractory to electrical pacing methods prior to the administration of disopyramide. With one exception, the QRS width (147 to 185 ms) and tachycardia cycle length (342 to 385 ms) increased following disopyramide. No significant electrocardiographic or other side effects resulted from the administration of disopyramide in this group.

Blood pressure changes

In 47 cases, the fall of systolic blood pressure following the infusion of disopyramide did not exceed 20 mmHg and did not require intervention. In three patients, significant and symptomatic hypotension resulted which required the infusion of calcium, elevation of the foot of the bed, in one case DC countershock and in a further case additional treatment with intravenous adrenaline. The mechanism of hypotension in two patients was related to increases in the ventricular response to supra-ventricular arrhythmias and in one case to apparent electromechanical dissociation.

Discussion

The direct effect of disopyramide tends to slow the discharge frequency of acute automatic foci (Sekiya & Vaughan-Williams, 1963; Sasyniuk & Kus, 1976), and by its membrane stabilizing (class I) effect (Vaughan-Williams, 1975), to slow conduction velocity in myocardial and specialized conducting

Figure 7 Surface electrocardiogram demonstrating a broad complex ventricular tachycardia with independent atrial activity before (a) and after (b) the infusion of disopyramide (2 mg/kg i.v.). Before the tachycardia terminates, its rate falls from 175 beats/min to 145 beats/min and the tachycardia QRS complex broadens from 0.13 s to 0.15 s.

tissue (Sasyniuk & Kus, 1976). Disopyramide also increases action potential duration (Sekiya & Vaughan-Williams, 1963) and tissue refractoriness (Gough, Driefus, De Azevedo & Katz, 1974; Danilo & Rosen, 1976) in *in vitro* preparations. In man, the drug has been shown to increase the refractory period of the atrial and ventricular myocardium (Befeler, Castellanos, Wells, Vaguero, Yen & Myerburg, 1975; Josephson, Caracta, Lau, Gallagher & Damato, 1973) and direct A-V anomalous bundles (Spurrell, Thorburn, Camm, Sowton & Deuchar, 1975; Camm & Spurrell, 1977). The effect on the A-V node is variable and depends on the balance between the direct and anti-cholinergic effects of the drug (Birkhead & Vaughan-Williams, 1977).

On the basis of these observations, it would be expected that disopyramide may slow or terminate automatic tachycardias and that tachycardias due to a re-entrant circus mechanism would be slowed or extinguished by collision between the advancing depolarization wave front and its receding refractory tail (Figure 8). However, if the increased tachycardia cycle length is greater than the increased refractoriness of any component of the circuit, the tachycardia will not terminate. Almost all paroxysmal re-entrant tachycardias in this series slowed in response to disopyramide, but only 64% terminated.

The anticholinergic effect of disopyramide has been variously estimated to be 1/1200th to 1/200th of the strength of atropine (Jequier, Deraedt, Plongeron & Vannier, 1970; Baines *et al.*, 1976). The administration of 150mg disopyramide could be the anticholinergic equivalent of up to 450 µg atropine. This anti-cholinergic effect may increase A-V conduction capacity and in the case of rapid supraventricular arrhythmias with a 2 : 1 or greater

Figure 8 This series of diagrams illustrates theoretical methods of drug termination of the atrioventricular re-entrant tachycardia associated with the Wolff-Parkinson-White syndrome. The size of the circle represents the cycle length of the tachycardia and the size of the blocks representing the atrioventricular node (ANV) and the anomalous pathway (AP) indicates their relative refractory states. In panel a the established tachycardia is illustrated. In panel b the effect of verapamil (left) and disopyramide (right) is diagrammed. Panel c shows the effect of atropine (left) and an alternative mode of action of disopyramide (right) as illustrated in Figure 6).

conduction ratio, the combination of decreased tachycardia cycle length and improved A-V nodal conduction may result in increased ventricular rates reminiscent of the effect of quinidine (Katz & Pick, 1969). In the absence of anomalous A-V bundles (Wolff-Parkinson-White syndrome) this potential hazard may be obviated by concomitant administration of A-V nodal blocking drugs such as verapamil, digoxin or β -adrenoceptor blockers. When supraventricular tachycardias present with 1:1 A-V conduction intravenous disopyramide does not result in increased ventricular rates. This is best illustrated in atrial flutter associated with the Wolff-Parkinson-White syndrome where a 1:1 conduction ratio is common (Figure 4).

Of the tachycardias tested, intravenous disopyramide best terminated paroxysmal ventricular tachycardia, atrial fibrillation and atrial tachycardia. Paroxysmal atrial flutter and re-entrant atrio-ventricular tachycardia associated with the Wolff-Parkinson-White syndrome responded less predictably.

In this series, paroxysmal atrial fibrillation was terminated in 71% of patients which represents a higher success rate than reported in other series (Luoma, Kujala, Juustila & Takkenen, 1978; Mizgala & Huvelle, 1976; Vandenbosch, Lisin, Andriange, Gach & Carlier, 1975). However, previous studies have included patients with both recent onset and chronic atrial fibrillation often in association with heart disease. In addition the number of patients with paroxysmal atrial fibrillation has been small.

There is very little comment in the literature about the effect of intravenous disopyramide on acute atrial flutter, and in those reports which do include patients with this arrhythmia the results are not distinguished from those obtained in atrial fibrillation (Luoma *et al.*, 1978). In addition the duration of the arrhythmia is not clearly stated. In one study (Vandenbosch *et al.*, 1975) only one of six patients with paroxysmal atrial flutter not associated with coronary artery disease responded to disopyramide.

There is a similar scarcity of information regarding paroxysmal atrial tachycardia and it has not been clearly distinguished from paroxysmal intranodal or atrioventricular tachycardia. This distinction is of some importance because the effect of intravenous disopyramide may be very different in each of these arrhythmias for reasons discussed above. The results obtained in patients with paroxysmal atrioventricular tachycardia in the WPW syndrome are similar to those demonstrated in previous reports (Spurrell *et al.*, 1975; Camm & Spurrell, 1977). In one case, however, there was marked acceleration of the tachycardia prior to termination. This was largely due to shortening of the A-V nodal conduction time, presumably a direct result of the anticholinergic effect

of disopyramide, similar to that of atropine (Akhtar, Damato, Caracta, Batsford, Josephson & Lau, 1974). Since atropine does not shorten the refractory period of the bypass tract (Wellens, 1975) an increase in the anterograde conduction velocity may result in a faster circulating impulse encountering block in the retrograde limb (anomalous connection) of the tachycardia circuit. This mechanism is illustrated diagrammatically in Figure 8.

The effectiveness of intravenous disopyramide in the termination rather than the prophylaxis of ventricular tachycardia (Orning, 1976; Vismara, Vera, Miller & Mason, 1977) has not been widely investigated. When it is clear that disopyramide has been given during tachycardia the success rate of termination has been up to 100% in some series (Mizgala & Huvelle, 1976). However, it is not always stated whether any or all of those patients were suffering from acute myocardial infarction. Other authors have reported success rates from 36% (Vogel, Desoutter, Bellanger, Motte & Wesli, 1976) to 69% (Valere, Guerot, Fenoy, Branvin, Urbanczyk & Tricot, 1977).

Two recent studies have examined the electrophysiological effects of disopyramide administered during ventricular tachycardia not associated with myocardial infarction (Gallagher, Pritchett, Benditt & Wallace, 1977; Camm, Ward & Spurrell, 1978). We have observed similar results to those of Gallagher and his colleagues (1977). Tachycardia slowed in all but one of our patients and was associated with broadening of the QRS complex. Termination by intravenous disopyramide achieved in 73% of cases. It appears that disopyramide, by slowing the tachycardia rate may facilitate termination by pacing techniques, for example, overdrive pacing (Denes, Wu, Dhingra, Amat-y-Leon, Wyndham, Moutner & Rosen, 1976; MacLean, Cooper, James & Waldo, 1977) as used in our patients.

Although disopyramide directly depresses the slope of spontaneous diastolic depolarization (Sasyniuk & Kus, 1976) its anticholinergic effect tends to prevent slowing of sinus node discharge (Birkhead & Vaughan-Williams, 1977). Initial observations (Befeler *et al.*, 1975) showed that disopyramide does not prolong and may shorten sinus node recovery time following overdrive suppression (Mandel, Hayakawa, Danzig & Marcus, 1971). More recent studies have confirmed these results in patients with normal sinus node function but have suggested that the compromised sinus node may be depressed by disopyramide (Reid, Williams & Parashar, 1977). A paroxysmal tachycardia which results in rapid atrial rates may *itself* cause overdrive suppression of the sinus node resulting in long pauses following termination. It is also appreciated that sinus node recovery times may be paradoxically prolonged following the administration of atropine (Gupta,

Lichstein, Chadda & Badvi, 1974). It has been suggested that this is due to improved atrio-sinal conduction and may presumably occur with other drugs possessing anticholinergic activity. In addition, it has been shown that small doses of atropine (less than 0.3 mg) may cause paradoxical slowing of the sinus rate (Das, Talmers & Weissler, 1975). These reasons may partially explain why normal sinus rhythm did not resume immediately following cessation of tachycardias involving the atria in six of our patients. In two of these there was persistent sinus bradycardia and in one other significant sinus arrest occurred with a 6 s period of ventricular asystole.

One other important electrocardiographic sequel to the use of disopyramide was noted in this series. In one example high grade A-V block followed termination of paroxysmal atrial fibrillation by disopyramide which has been reported to impair conduction within the His-Purkinje system (Josephson *et al.*, 1973) and this effect may have been responsible for the development of A-V block in our patient.

It is always difficult to ascribe with certainty the

termination of paroxysmal arrhythmia to pharmaceutical intervention (Hill, 1970). By definition, paroxysmal arrhythmias do terminate spontaneously. In this study each arrhythmia was observed for at least 5 min prior to drug treatment and clinically all patients suffering spontaneous tachycardias had had symptoms, which could reasonably be ascribed to the arrhythmia, for at least 1 hour. The sequence of events prior to termination and at termination suggest that the drug was usually relevant to the termination of the arrhythmia. For example, slowing of rate, prior to cessation of tachycardia, was uniformly observed in patients with paroxysmal atrial or ventricular tachycardia.

Overall, disopyramide phosphate proved a successful antiarrhythmic agent for the termination or amelioration of a variety of paroxysmal tachycardias, but the occurrence of side effects related to its use demands some caution. Not only the electrocardiographic side effects, but also its mechanism of action as an antiarrhythmic agent must, in part, be explained by the anticholinergic properties of the drug.

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