COMBINED EFFECT OF VERAPAMIL AND DISOPYRAMIDE ON INDUCTION OF CIRCUS MOVEMENT TACHYCARDIA IN PATIENTS WITH PRE-EXCITATION

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By means of intracardiac recordings and programmed electrical stimulation of the heart, the combination effect of verapamil and disopyramide on induction of circus movement tachycardia was studied in 8 patients with anomalous extranodal atrioventricular (A-V) pathway. In 4 of 6 patients who manifested reproducible circus movement tachycardia, verapamil, 0.2 mg/kg intravenously administered, prevented the induction of tachycardia by increasing the A-V nodal refractoriness. Disopyramide in a dose of 2 mg/kg was injected 30 minutes after the start of verapamil administration, when prolongation of the A-V nodal conduction time (A-H interval) had continued in most of the patients. Disopyramide lengthened the effective refractory period of the anomalous pathway in all patients in whom this could be determined. The A-H interval, which had been prolonged by verapamil, was shortened in 4 patients and almost unchanged in the remaining 4. After addition of disopyramide, sustained tachycardia could be induced in 2 patients who had lost the ability of initiating circus movement tachycardia after verapamil administration. Thus, disopyramide, when administered together with verapamil, may block the effect of verapamil on the A-V node by its anticholinergic action. A concomitant prescription of disopyramide with verapamil in expectation of the depression of both the anomalous pathway and the A-V node may have an untoward outcome.

THE circus movement tachycardia associated with the Wolff-Parkinson-White syndrome usually involves antegrade conduction by way of the A-V node—His pathway and retrograde conduction by way of the anomalous pathway. Any therapeutic agent which prolongs the refractoriness of one pathway of the reciprocal circuit may be useful in management of tachycardia of this

sort. Wellens¹ has recommended the combination of a drug which prolongs the refractory period of the anomalous pathway with a drug which prolongs the refractory period of the A-V node, in cases where single drug therapy fails. However, little information is available regarding the combined effect of drugs acting on different parts of the reciprocal circuit. In this study, we report the combined effect of verapamil and disopyramide, a quinidine-like drug, on induction of circus movement tachycardia in patients with anomalous pathways.

Key Words:

Verapamil
Disopyramide
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TABLE I CLINICAL DETAILS OF PATIENTS

Case No.	Age	Sex	Diagnosis
1	20	M	Type A WPW syndrome
2	14	F	Type A WPW syndrome
3	33	F	Type A WPW syndrome
4	27	M	Intermittent Type A WPW syndrome
5	52	F	Intermittent Type A WPW syndrome
6	37	M	Concealed left-sided Kent bundle
7	28	M	Type B WPW syndrome
8	17	F	Type B WPW syndrome

PATIENTS AND METHODS

Eight patients with anomalous extranodal A-V pathways were studied; their ages ranged from 14 to 52 years; 4 were male and 4 were female (Table I). Five had constant pre-excitation (Cases 1, 2, 3, 7 and 8). Two had intermittent pre-excitation (Cases 4 and 5). One patient (Case 6) had no electrocardiographic evidence of pre-excitation, but did have a left-sided anomalous pathway that conducted only in a retrograde direction²⁻⁶. All had a documented history of tachycardia with a normal QRS configuration.

Informed consent was obtained from each patient or from the parents. All patients underwent the electrophysiological study in the post-absorptive non-sedated state. All antiarrhythmic drugs were discontinued at least 48 hours before the study. Three electrode catheters were introduced into the right saphenous vein. A quadripolar catheter was positioned against the lateral wall of the high right atrium. The proximal 2 electrodes were used to pace the atrium and the distal 2 electrodes were used to record high right atrial electrograms. A tripolar or quadripolar catheter was placed across the tricuspid valve to record the His bundle electrogram. A bipolar catheter was positioned in the right ventricular apex for ventricular pacing. A bipolar esophageal electrogram (filter setting of 10 to 500 HZ) was used for recording of the left atrial electrical activity.⁷ The intracardiac electrograms were recorded simultaneously with the esophageal electrogram and standard electrocardiographic leads, I, aV_F, and V₁ on a multichannel oscilloscopic photographic recorder (Electronics for Medicine, VR-12) at a paper speed of 100 mm/sec with filter settings of 30 to 500 HZ. Stimuli of 1 msec duration and twice diastolic threshold strength were delivered by a programmable

cardiac stimulator (ME 514, manufactured by Metro Electric Co., Kyoto).

Incremental atrial and ventricular pacing was performed up to a maximal heart rate of 150 or 160 per minute. Antegrade conduction time in the anomalous pathway was measured from the stimulus artifact of the atrially driven beats to the onset of the delta wave on the surface electrocardiogram. The ventriculoatrial conduction time was measured from the ventricular stimulus artifact to the earliest onset of retrograde atrial activation. Fixed ventriculoatrial conduction time during incremental ventricular pacing and abnormal retrograde atrial activation sequence was demonstrated in all cases. This suggests a dominant retrograde conduction over the anomalous pathway^{8,9}. We regarded the ventriculoatrial conduction time measured at a ventricular paced rate of 150 per minute to be the retrograde conduction time in the anomalous pathway.

The effective refractory periods of the A-V node and antegrade anomalous pathway were determined, using the atrial extrastimulus method, with test stimuli delivered after every 10th driven beat. The retrograde effective refractory period of the anomalous pathway was also measured at a comparable basic paced cycle length. The effective refractory period of the A-V node was defined as the longest atrial coupling interval that does not result in conduction of a premature atrial beat to the His bundle. The antegrade or retrograde effective refractory period of the anomalous pathway was defined as the longest atrial or ventricular premature beat interval at which a premature beat failed to conduct through the anomalous pathway either antegradely or retrogradely. The criteria for conduction occurring retrogradely in an anomalous pathway have been described previously by

TABLE II EFFECTIVE REFRACTORY PERIOD (msec) OF ANOMALOUS PATHWAY AND ATRIOVENTRICULAR NODE

Case No.	Basic cycle length	ERP AP antegrade			ERP AP retrograde			ERP AVN		
		C	V	D	C	V	D	C	V	D
1	500	235	230	<255	260	265	290	>235	>230	?
2	460	230	235	blocked	255	245	365	<200	>235	<235
3	550	290	295	340	<240	<240	<250	250	>295	300
4	500	—	—	—	235	230	275	280	275	275
5	600	—	—	—	340	300	345	315	440	360
6	500	—	—	—	265	260	285	245	345	280
7	550	265	260	300	<210	<205	<225	>265	>260	>300
8	600	310	300	345	<260	<240	<270	>310	>300	>345
Mean		266.0	264.0	328.3	271.0	260.0	312.0	272.5	353.3	303.8
± SD		34.5	32.7	24.7	40.2	26.2	40.3	32.3	82.8	39.0
P (paired t test)		NS (n = 5) < 0.01 (n = 3)			NS (n = 5) < 0.05 (n = 5)			NS (n = 3) NS (n = 3)		

Abbreviations: ERP = effective refractory period; AP = anomalous pathway; AVN = atrioventricular node; C = control; V = verapamil; D = disopyramide; SD = standard deviation; NS = not significant

Wellens and Durrer¹⁰

After control studies were completed, 0.2 mg/kg body weight of verapamil was given intravenously over a period of 3 minutes. Repeat measurements were initiated 5 minutes after the start of the drug administration and completed within 25 minutes. Disopyramide in a dose of 2 mg/kg body weight was added intravenously 30 minutes after the start of the administration of verapamil and measurements were then repeated. Statistical evaluation was performed with Student's t-test for paired samples.

RESULTS

Effective Refractory Period of Anomalous Pathway (Table II)

The antegrade effective refractory period of the anomalous pathway could be measured in 4 of the 7 patients with manifest pre-excitation. (In 2 patients, intermittent pre-excitation during the study precluded measurement of the antegrade refractory period of the anomalous pathway. In one patient, atrial refractoriness limited the measurement of the anomalous pathway antegrade refractory period after disopyramide.) Following verapamil no change of more than 10 msec was observed. Temporary complete block of antegrade conduction occurred in one patient after disopyramide. In the remaining patients, disopyramide lengthened the antegrade refractory period of the anomalous pathway by 40 to

45 msec ($p < 0.01$). The retrograde effective refractory period of the anomalous pathway could be measured in 5 patients. In 3 patients, ventricular refractoriness limited determination of the anomalous pathway retrograde refractory periods. Only minor changes were observed after verapamil administration except in one patient. Disopyramide prolonged the retrograde refractory period of the anomalous pathway by 25 to 120 msec in each patient ($p < 0.05$).

Conduction Times in the Anomalous Pathway (Table III)

Table III summarizes the effects of verapamil and disopyramide on the antegrade and retrograde conduction times in the anomalous pathway. In 3 patients, pre-excitation was not evident during the atrial pacing. After verapamil, both antegrade and retrograde conduction times were almost unchanged. After disopyramide, temporary but complete block in the anomalous pathway occurred in one patient antegradely and in 2 retrogradely, at the test cycle length. In the other patients, disopyramide prolonged the antegrade conduction time by 20 to 35 msec ($p < 0.02$) and the retrograde conduction time by 15 to 45 msec ($p < 0.01$).

A-H interval (Table IV)

Table IV summarizes the results of the measurements of the A-H interval. In 3 patients in whom measurement of the A-H interval was

TABLE III ANTEGRADE AND RETROGRADE CONDUCTION TIMES (msec) IN ANOMALOUS PATHWAY

Case No.	Basic cycle length	Antegrade conduction times			Basic cycle length	Retrograde conduction times		
		C	V	D		C	V	D
1	500	100	100	120	400	180	180	210
2	460	90	90	blocked	400	140	140	blocked
3	550	140	140	160	400	150	150	180
4	600	—	—	—	400	210	210	blocked
5	600	—	—	—	400	155	155	200
6	500	—	—	—	400	210	210	245
7	550	120	120	140	400	150	145	160
8	600	145	145	180	400	170	170	195
Mean		119.0	119.0	150.0		170.6	170.0	198.3
± SD		24.1	24.1	25.8		27.3	27.9	28.8
P (paired t test)		NS (n = 5) < 0.02 (n = 4)				NS (n = 8) < 0.01 (n = 6)		

Abbreviations as the same as shown in Table II.

TABLE IV A-H INTERVALS (msec)

Case No.	Basic cycle length	Control	After V		After D
			5 min	30 min	5 min
1	NSR	85	110	110	90
2	460	60	110	60	60
3	NSR	90	125	115	115
4	500	90	85	90	85
5	600	135	190	170	175
6	500	60	90	90	75
7	NSR	65	90	90	75
8	600	135	165	165	130
Mean		90.0	120.6	111.3*	100.6
± SD		30.5	38.1	38.4	37.6
P (paired t test)			< 0.01 (n = 8)		NS (n = 8)

*Significantly different from control; $p < 0.01$ (n = 8).

Abbreviations: NSR = normal sinus rhythm; for others see Table II.

impossible after verapamil (because the His bundle electrogram was buried in the ventricular complex during atrial pacing) the values obtained during sinus rhythm are shown. The A-H interval was prolonged in 7 of 8 patients after verapamil ($p < 0.01$). This prolongation continued until the start of the administration of disopyramide in all but one patient (Case 2) in whom it returned to the control value ($p < 0.01$, compared to control). In 4 patients, the A-H interval decreased by 15 to 30 msec after disopyramide. In the remaining 4, no change of more than 5 msec was observed.

Effective Refractory Period of the A-V Node (Table II)

The effective refractory period of the A-V node could be determined in 4 patients during the control study. (In 3 patients, the effective refractory period of the A-V node was longer than that of the anomalous pathway. In one patient, atrial refractoriness limited the measurement of the refractory period of the A-V node.) Verapamil lengthened the effective refractory periods of the A-V node in 4 of 5 patients for whom the values before and after the drug could be compared. In these patients, the refractory

TABLE V INDUCTION OF CIRCUS MOVEMENT TACHYCARDIA (CMT)

Case No.	Mode of CMT Initiation			Cycle Length of CMT (msec)		
	C	V	D	C	V	D
1	VPB, rapid ventricular pacing	—	VPB, rapid ventricular pacing	335	—	385
2	APB	—	—	305	—	—
3	APB	VPB*	APB*	390	460	430
4	APB, rapid atrial pacing	APB, rapid atrial pacing	—	360	365	—
5	—	—	APB*	—	—	450
6	APB	—	—	265	—	—
7	—	—	—	—	—	—
8	VPB	—	VPB	430	—	440

*Tachycardia did not last more than 30 seconds.

Abbreviations: VPB = ventricular premature beat; APB = atrial premature beat; for others see Table II.

period of the A-V node decreased after disopyramide, though it was still longer than the control value. Such a decrease might be attributed to an atropine-like action of disopyramide¹¹ or to a time lapse while the effect of verapamil decreased.

Effect on Induction of Circus Movement Tachycardia (Table V)

Sustained tachycardia could be induced in 6 patients before verapamil administration, using the following techniques: (1) premature atrial stimulation in 4; (2) rapid atrial pacing in one; (3) premature ventricular stimulation in 2; (4) rapid ventricular pacing in one. In all patients, the induced tachycardia was characterized by antegrade conduction in the A-V node—His system and retrograde conduction in the anomalous pathway.

In 4 of these 6 patients (Cases 1, 2, 6 and 8), the ability to induce circus movement tachycardia was lost after verapamil administration. This loss represented an increase in the antegrade refractory period of the A-V node that eliminated the atrial or ventricular echo zone (Cases 1, 2 and 8) or that prevented multiple sequential antegrade normal pathway conduction (Case 6). In 2 patients, induction of circus movement tachycardia was possible both before and after verapamil by identical stimulatory techniques (Case 4) or by others (Case 3). In Case 3, tachycardia could not be induced by atrial premature stimulation, because the effective refractory period of the

A-V node exceeded the antegrade effective refractory period of the anomalous pathway after verapamil. However, induction of tachycardia by premature ventricular stimulation was possible, thereby suggesting lengthening of the effective refractory period of the A-V node—His pathway for retrograde conduction after verapamil. The tachycardia cycle length was prolonged (460 msec as compared with 390 msec before the injection) and the tachycardia was terminated spontaneously with a block in the antegrade pathway.

Disopyramide prevented the initiation of tachycardia in one patient (Case 4) in whom verapamil was not effective. After disopyramide administration, tachycardia could be initiated in 4 patients (Cases 1, 3, 5 and 8). In 2 of these 4 (Cases 3 and 5), tachycardia did not last more than 30 seconds because of an A-V block. In Case 5, though an atrial premature beat induced only one or two re-entrant echo beats over the anomalous pathway retrogradely before disopyramide administration, tachycardia could be initiated after disopyramide. In the other 2 patients (Cases 1 and 8), the ability to induce sustained circus movement tachycardia was lost after administration of verapamil and reappeared after the addition of disopyramide (Fig. 1). In Case 8, during the control study, the tachycardia zone was defined between premature ventricular coupling intervals of 450 and 350 msec. Earlier premature beats elicited at coupling intervals of 340 to 260 msec did not initiate tachycardias. After disopyramide, the tachycardia zone shifted

Fig.1. Case 8. Effect of verapamil and disopyramide on induction of circus movement tachycardia. From top to bottom in each panel, electrocardiographic leads, I, AV_F and V₁, bipolar esophageal electrogram (E), His bundle electrogram (HBE) and high right atrial electrogram (HRA) are shown. Paper speed was 100 mm/sec and time lines were at 1 sec. The basic paced cycle length was 600 msec. S₁, A₁ and V₁ represent stimulus artifact, atrial and ventricular electrograms of the basic driven beats, respectively. S₂, A₂ and V₂ represent the stimulus artifact, atrial and ventricular electrograms of the premature beats, respectively. Upper panel shows induction of sustained tachycardia during the control study by a ventricular premature beat elicited at coupling intervals (V₁V₂) of 380 msec. The tachycardia zone was defined between V₁V₂ intervals of 450 and 350 msec. Middle panel shows loss of ability to induce tachycardia after verapamil. A₂ is not followed by His bundle electrogram (H), suggesting increased refractoriness in the A-V node. Lower panel shows induction of sustained tachycardia after additional administration of disopyramide at a V₁V₂ interval of 300 msec. The tachycardia zone shifted to 350 to 270 msec after disopyramide, suggesting shortening of the effective refractory periods of the A-V node, in both directions.

to 350 to 270 msec. The induction of tachycardia was possible until the ventricle became refractory. We assumed that during the control study, A-V nodal refractoriness produced by the retrograde penetration of the last basal ventricular response prevented the transmission of an impulse across the A-V node in an antegrade direction and thus a circuit of reciprocating tachycardia could not be established between premature ventricular coupling intervals of 340 and 260 msec. Because the effective refractory period of the A-V node decreased after disopyramide, the subsequent atrial activation in response to earlier ventricular premature beats *via* the anomalous pathway found the A-V node already out of the refractory period, and tachycardia occurred. The fact that the latest ventricular premature beat able to initiate tachycardia was evidenced earlier after disopyramide administration suggests that disopyramide resulted in shortening of the effective refractory period of the A-V node for retrograde conduction as well as for antegrade conduction.

DISCUSSION

Paroxysmal supraventricular tachycardia complicating the pre-excitation syndrome usually reflects circus movements, with the normal pathway (the A-V node—His system) as the antegrade limb and the anomalous pathway as the retrograde limb. The ability to induce circus movement tachycardia in a patient with two pathways (anomalous pathway and normal pathway) depends on unidirectional block of a premature impulse in one limb and critically slow conduction in the contralateral limb, allowing the limb with unidirectional block to recover for reciprocal conduction.

Pharmacological therapy of circus movement tachycardia may be aimed at reducing the number of premature beats, narrowing the echo zone (interval during which premature beats can dissociate the normal and anomalous pathways) and prolonging refractoriness so that the returning impulse is blocked either in the anomalous pathway or the normal pathway.

The effects of several different drugs have been studied in patients with the pre-excitation syndrome undergoing electrophysiological investigations. Procainamide, quinidine and other quinidine-like drugs can prevent circus movement tachycardia in patients with a retrogradely conducting anomalous pathway by increasing refrac-

toriness of the anomalous pathway, ventricle and atrium.¹²⁻¹⁴ On the other hand, drugs such as digitalis or verapamil which act predominantly on the A-V node are effective because of their blocking action on the antegrade pathway of circus movement tachycardia.¹⁵⁻¹⁹

It is often difficult to manage with a single drug circus movement tachycardia associated with the pre-excitation syndrome. Wellens¹ has recommended dosing with a combination of a drug which prolongs the refractory period of the accessory pathway with a drug which prolongs the refractory period of the A-V node, in cases where single drug therapy fails. In this study, disopyramide, a quinidine-like drug,²⁰⁻²³ was administered 30 minutes after the start of the administration of verapamil to evaluate the combined effect on induction of circus movement tachycardia associated with the pre-excitation syndrome. Like previous workers,^{16-19,24,25} we have observed that verapamil affects mainly the A-V node and only minimally the anomalous pathway, while disopyramide has a depressant effect on the anomalous pathway.

As shown in Table IV, the A-H interval was prolonged in 7 of 8 patients after verapamil and remained lengthened until the start of the administration of disopyramide in all patients except one, in whom it returned to the control value. This suggests that in most patients, the depressant effect of verapamil on the A-V node persisted until the start of the administration of disopyramide.

The effects of disopyramide on A-V conduction and refractory periods are varied.^{24,26-28} Birkhead and Vaughan Williams²⁹ showed that disopyramide prolonged the A-H interval and increased A-V refractoriness when administered after atropine pretreatment. Hence it is suggested that the variability of the electrophysiological responses of the A-V node to disopyramide may be the result of an anticholinergic action of disopyramide. Such would shorten the A-H interval and the refractory periods of the A-V node, particularly if the vagal tone was high, hence the direct depressant effect of disopyramide would be masked.

In 2 (Cases 1 and 8) of 4 patients in whom verapamil prevented circus movement tachycardia, the ability to induce sustained tachycardia reappeared after the additional administration of disopyramide. In these patients, the effective refractory period of the A-V node could not be measured. However, the fact that the A-H

interval returned to the control value immediately after the administration of disopyramide suggests that disopyramide blocked the effect of verapamil on the A-V node by its anticholinergic action. In Case 8, as described above, a shift of the tachycardia zone to the left (to shorter premature beat interval) after disopyramide represents a shortening of the effective refractory periods of the A-V node, in both the antegrade and retrograde directions.

We observed a significant increase in the conduction time and the antegrade and retrograde effective refractory periods of the anomalous pathway after disopyramide, and previous workers have shown that disopyramide prolongs atrial and ventricular refractoriness.^{24,26,28,29} It would, therefore, be reasonable to expect disopyramide to be of value in the prevention of circus movement tachycardia in patients with anomalous pathway. The effect on retrograde conduction ranged from total block (Cases 2 and 4) to minimal effect (Case 5, compared to control). In Case 4, disopyramide could prevent the initiation of tachycardia, while verapamil was not effective. If disopyramide dose not sufficiently prolong the anomalous pathway retrograde refractory period, there is a risk of actually favoring initiation of tachycardia rather than preventing it by slowing retrograde conduction to allow sufficient time for the A-V node to recover (as in Case 5).

In some patients, as shown in this study, disopyramide may be disadvantageous in the management of tachycardia, due to an anti-cholinergic action which shortens the effective refractory period of the A-V node. Although the efficacy of disopyramide in the suppression of spontaneous premature beats which act as a triggering mechanism of tachycardia³⁰⁻³² may offset this disadvantage in actual clinical situations, the combined administration of disopyramide with a drug that affects the A-V node should be done with caution.

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