Treatment of recurrent sustained ventricular tachycardia with mexiletine and disopyramide

Control by programmed ventricular stimulation

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SUMMARY Oral antiarrhythmic treatment with mexiletine and disopyramide was evaluated in 34 patients with recurrent sustained ventricular tachycardias by programmed ventricular stimulation, except in a few instances where spontaneous attacks occurred under therapy. Coronary heart disease was present in 17 patients, cardiomyopathy in 11, myocarditis in five, and mitral valve prolapse in one. Complete suppression of ventricular tachycardia was observed in three of 30 patients under mexiletine and in one of 25 patients under disopyramide. Disopyramide slowed the rate of the ventricular tachycardia considerably, while mexiletine had no such influence. For a mean of 24 months, 19 patients were maintained on either substance. Complete suppression of ventricular tachycardia during programmed stimulation predicted freedom from recurrences. Ventricular tachycardias recurred less frequently and at a slower rate in the other patients, but 31% have died. This study shows that complete suppression of ventricular tachycardia by mexiletine or disopyramide can be achieved only in a minority of patients with previously drug-resistant tachycardias.

Recurrent ventricular tachycardias are associated with a high mortality in patients with underlying heart disease.¹⁻² Since empirically chosen antiarrhythmic drug treatment is often ineffective, electrophysiological testing of such drug treatment was proposed for these patients.³⁻⁵ Nevertheless, the choice of antiarrhythmic drugs remains empirical, and the comparative efficacy of customarily used drugs for control of sustained ventricular tachycardias has not yet been readily assessed. Therefore, this study compares the effects of the commonly used antiarrhythmic agents mexiletine and disopyramide on inducibility and rate of recurrent sustained ventricular tachycardia.

Patients and methods

Mexiletine and disopyramide were given to 34 out of 45 patients, who underwent consecutive electrophysiological studies for the evaluation of recurrent persistent ventricular tachyarrhythmias between May

1979 and August 1981. The clinical data of these 34 patients are listed in Table 1. All patients except case 8 had been referred to our institution from other hospitals for comprehensive evaluation and prescription of antiarrhythmic drugs. All patients had at least one documented spontaneous episode of symptomatic ventricular tachycardia (ranging from one to 80) that was sustained for minutes and usually required pharmacological or electrical conversion (mean DC cardioversions 5.9, ranging from 0 to 45).

One to eight different antiarrhythmic drugs were applied before patients entered the study (Table 1). Drugs listed were considered ineffective when sustained ventricular tachycardia or numerous complex ventricular arrhythmias recurred under these agents.

Coronary arteriography and contrast left ventriculograms were performed in 32 patients. The underlying cardiac disease was coronary artery disease in 17 patients, congestive cardiomyopathy in nine, hypertrophic non-obstructive cardiomyopathy in two, history of myocarditis in five, and mitral valve prolapse in one patient. No patient was included with non-sustained ventricular tachycardia, acute myocardial infarction, prolonged QT syndrome, or electro-

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Table 1 Clinical data of 34 patients with recurrent sustained ventricular tachycardia

Case No.	Age (y)	Sex	Cardiac diagnosis	NYHA classification	Ventricular tachycardia				Previous antiarrhythmic drugs
					Cycle length (ms)	Morphology	Previous occurrence	Previous DC cardioversion	
1	54	M	CAD	III	260	LBBB	35	23	L, ajm, diso, propa, proc
2	67	M	CAD	III	316	LBBB	15	5	Quin, V, ajm, apr
3	50	M	CAD	III	333	RBBB	10	3	L, quin, apr, V, diso
4	57	M	CAD	II	316	LBBB	8	6	L, propa, DPH, apr
5	42	M	HNOCM	II	333	LBBB	60	1	Ajm, propa, L, V
6	63	M	CAD	II	316	Rhythm strip	9	1	Propa
7	50	F	CCM	III	280	RBBB	50	30	L, propa, apr, ajm, DPH, lorc
8	60	F	CCM	III	333	LBBB	2	2	L, quin, apr, ajm, propa, V
9	51	M	CCM	III	300	LBBB	6	1	Ajm, L, apr
10	66	M	CAD	III	375	RBBB	17	15	Ajm, apr, L, quin
11	76	M	CAD	III	250	LBBB	11	1	Amio, L, propa, apr, V
12	53	M	CAD	II	250	LBBB	3	1	Ajm, V, proc, L
13	63	M	CCM	III	345	RBBB	22	0	L, apr, propa, ajm, V
14	58	M	MC	II	280/240	RBBB/LBBB	5	0	Quin
15	35	M	CCM	II	300	LBBB	50	1	Propa, ajm, apr, quin, L, proc, lorc, V
16	43	M	CCM	IV	285	LBBB	4	1	Quin, propa, ajm, L, V
17	46	M	MC	II	353	LBBB	5	0	Quin, propa, apr, L, ajm
18	33	M	MC	II	316	LBBB	6	0	Quin, propa, L
19	56	M	CAD	III	340	LBBB	2	1	Ajm, L, propa, apr, V
20	52	M	CAD	II	300	RBBB	6	4	L, ajm, lorc, propa
21	52	M	CAD	II	230	RBBB	4	0	L, V, propa
22	65	M	CCM	III	240/333	LBBB/RBBB	70	45	Ajm, propa
23	65	M	CCM	III	300	RBBB	60	1	L, ajm, propa
24	46	M	CAD	II	316	LBBB	15	11	L, propa, apr, V
25	70	M	CAD	III	500	RBBB	8	0	V, L, ajm
26	27	M	CCM	II	200	Rhythm strip	24	10	L, ajm, diso, lorc, V
27	69	M	CAD	III	214	LBBB	4	2	L, ajm, propa, diso
28	62	M	CAD	II	316	LBBB	3	0	L, ajm
29	27	M	MC	I	250	LBBB	4	0	L, ajm, propa
30	41	M	MC	III	286	LBBB	16	8	Lorc, L, mex
31	59	M	CAD	II	273	RBBB	5	0	V, L, ajm, lorc
32	45	M	HNOCM	II	285	LBBB	50	0	Ajm, apr, quin, propa, mex
33	46	F	MVP	II	200	LBBB	7	5	L, V, mex, toc
34	61	F	CAD	IV	333	RBBB	80	25	L, ajm, mex, propa

CAD, coronary artery disease; CCM, congestive cardiomyopathy; HNOCM, hypertrophic non-obstructive cardiomyopathy; MC, history of myocarditis; MVP, mitral valve prolapse; ajm, ajmaline; apr, aprindine; diso, disopyramide; DPH, diphenylhydantoin; L, lignocaine; lorc, lorcinide; mex, mexiletine; propa, propafenone; proc, procainamide; quin, quinidine; toc, tocainide; V, verapamil

lyte disturbances. The clinical status, when free of arrhythmias, was mostly class II or III according to the NYHA classification (see Table 1).

All patients gave informed written consent to the invasive electrophysiological evaluation of drug treatment. The electrophysiological studies were performed with the patient in a fasting, non-sedated state. Administration of antiarrhythmic drugs was discontinued at least 48 hours before the study; patients with amiodarone treatment in the past four weeks did not enter the study. Digitalis and propranolol were maintained at constant dosage until the evening before the study, which was performed in the morning. In the initial electrophysiological study, a hexapolar and a bipolar electrode catheter were inserted via the right femoral vein and left cubital vein and placed in the right atrium and just below the tricuspid valve, respectively, to record the His bundle activity.⁶ The electrode catheter thereafter was advanced to the apex of the right ventricle for ven-

tricular stimulation. Rectangular stimuli of twice diastolic threshold and 2 ms in duration were delivered by a battery-powered programmable stimulator (Medtronic Conduction System Analyzer model 5325).

After atrial stimulation had been performed, single premature ventricular extrastimuli (S_1S_2) were introduced in late diastole during regular right ventricular basic drive and moved earlier in steps of 10 ms until ventricular refractoriness was reached. Basic stimulation was performed with intervals slightly shorter than sinus rhythm, and with intervals of 600 ms, 500 ms, and 400 ms. If thereby ventricular tachycardia could not be induced, double premature impulses ($S_1S_2S_3$) were applied beginning at an S_1S_2 interval 20 to 30 ms longer than the right ventricular effective refractory period. The S_2S_3 interval was progressively shortened in steps of 10 ms until S_3 did not depolarise the ventricles. For serial electrophysiological testing, one electrode catheter was either left in place or was inserted again percutaneously.

Table 2 Results of oral treatment with mexiletine and disopyramide

Case No.	Mexiletine					Disopyramide					Plasma level (µg/ml)
	Cycle length (ms)	Induction	Morphology	Dose (mg/d)	Plasma level (µg/ml)	Cycle length (ms)	Induction	Morphology	Dose (mg/d)	Plasma level (µg/ml)	
1	272	Spontaneous	LBBB	800		333	Spontaneous	LBBB	600		
2	307	600 S ₁ S ₂	LBBB	800		420	600 S ₁ S ₂	LBBB	900		
3	400	500 S ₁ S ₂ S ₃	RBBB	800	1.37	500	600 S ₁	RBBB	900		
4	353	Atrial stimulation	LBBB	800		444	400 S ₁ S ₂	LBBB	900		
5	413	Spontaneous	LBBB	700		428	600 S ₁ S ₂	LBBB	600		
6	333	600 S ₁ S ₂	LBBB	800	0.52	333	400 S ₁ S ₂	LBBB	750		
7	300	500 S ₁ S ₂	RBBB	800		365	600 S ₁ S ₂	RBBB	600		
8	428	600 S ₁ S ₂	LBBB	600	2.1	400	400 S ₁ S ₂ S ₃	LBBB	600		
9	316	Spontaneous	LBBB	800		380*	600 S ₁ S ₂ S ₃	LBBB	600		
10	375	600 S ₁ S ₂	RBBB	600	1.89	480	500 S ₁ S ₂ S ₃	RBBB	450		
11	240	Spontaneous	LBBB	600		461	600 S ₁ S ₂	LBBB	500	4.35	
12	340	Catheter introduction	LBBB	600	0.96	365	600 S ₁ S ₂ S ₃	LBBB	600		
13	387	Spontaneous	RBBB	600	1.85	600	500 S ₁ S ₂ S ₃	RBBB	450		
14	300	600 S ₁ S ₂ S ₃	RBBB**	800	1.75	333	500 S ₁ S ₂ S ₃	RBBB	600		
15	300	600 S ₁ S ₂ S ₃	LBBB	800		324	Spontaneous	Rhythm strip	600	2.20	
16	300	Spontaneous	LBBB	600		333	Spontaneous	LBBB	600		
17	220	400 S ₁ S ₂ S ₃	LBBB	600	2.4	350	500 S ₁ S ₂	LBBB	750	2.92	
18	333	600 S ₁ S ₂ S ₃	LBBB	800		360	Atrial stimulation	LBBB	750		
19	200	500 S ₁ S ₂ S ₃	LBBB	800	1.25	300	400 S ₁ S ₂ S ₃	LBBB	600		
20	355	400 S ₁ S ₂ S ₃	RBBB	800		430	500 S ₁ S ₂ S ₃	RBBB	600	4.42	
21	250	400 S ₁ S ₂ S ₃	RBBB	800	1.27	310	400 S ₁ S ₂ S ₃	RBBB	750	2.98	
Mean±SD 320±62****						392±74****					
22	375	500 S ₁ S ₂ S ₃	RBBB**	800		—	—	—	—		
	292	500 S ₁ S ₂ S ₃	LBBB	800		—	—	—	—		
23	—	—	—	—		Non-inducible					
24	Non-inducible	—	—	—		—	—	—	—		
25	521	600 S ₁ S ₂	RBBB	800		—	—	—	—		
26	300	400 S ₁ S ₂ S ₃	RBBB	1000	1.57	—	—	—	—		
27	Non-inducible	—	—	—		—	—	—	—		
28	Non-inducible	—	—	—	0.76	—	—	—	—		
29	300	600 S ₁ S ₂ S ₃	LBBB	800	2.3	—	—	—	—		
30	316	Spontaneous	LBBB	600		—	—	—	—		
31	200	600 S ₁ S ₂ S ₃	RBBB	800		—	—	—	—		
32	—	—	—	—		300	500 S ₁ S ₂	LBBB	600	2.78	
33	—	—	—	—		300	Catheter introduction	LBBB	600		
34	—	—	—	—		440	Spontaneous	RBBB	600		

*Repetitive ventricular response.

**Two types of tachycardia with different morphology and rate were present; the prevailing form was considered for comparison.

***Plasma levels of disopyramide (normal range 2 to 5 µg/ml) were determined by Professor W Vogt, Institut f Klinische Chemie, University of Munich.

****Cohort treated with either drug.

DEFINITIONS

Sustained ventricular tachycardia was defined as a ventricular tachycardia that lasted for one minute or required programmed stimulation, drug administration, or DC cardioversion for termination.

Ventricular tachycardia was considered to be not sustained if it persisted for more than five beats and reverted spontaneously to original rhythm within one minute.

The initiation of three to five ventricular complexes was taken as repetitive response.

Complete suppression (non-inducible) was assumed if two or fewer ventricular responses were initiated by programmed stimulation.

According to previous clinical experience, mexiletine was administered as oral loading dose of 400

mg, followed by 600 to 1000 mg daily in three to four divided doses. The maintenance dose was given for at least four days. Disopyramide, 450 to 900 mg per day, was given for the same period. When drug action in the given ranges was unsatisfactory, no further trial with increased dose was performed.

At the end of the electrophysiological study, in some patients 5 ml blood samples were taken for determination of plasma levels of the drugs. The samples were centrifuged, and the plasma was removed and frozen at -25°C for subsequent analyses by gas chromatography (normal range 0.5 to 2.0 µg/ml mexiletine).^{7,8}

Statistical analysis was performed by the Friedman test for rank analysis and by the Wilcoxon matched-pairs signed-ranks test.⁹

Fig. 1 (A) Induction of ventricular tachycardia during control stimulation in a 50 year old patient with congestive cardiomyopathy (case 7). After basic stimulation with a cycle length of 400 ms, two premature stimuli initiate a ventricular tachycardia with a right bundle-branch block pattern and a mean cycle length of 280 ms. (B) Under mexiletine, 800 mg per day, the tachycardia is induced by one premature stimulus. The morphology of the tachycardia is almost identical with the one during control, and the cycle length is slightly longer. (C) Under disopyramide, 600 mg per day, a ventricular tachycardia with right bundle-branch block is induced as before, the mean cycle length being 365 ms.

Results

MEXILETINE

Mexiletine, 600 to 1000 mg per day, was given to 30 patients. Nevertheless, ventricular tachycardia recurred spontaneously in seven patients, in six it could be initiated by single premature stimuli, in 12 by double premature stimuli, and in two patients it recurred in response to atrial stimulation and to positioning of the electrode, respectively. In only three patients out of the 30 was ventricular tachycardia totally prevented by mexiletine. The rate of ventricular tachycardia was not influenced by mexiletine (cycle length $303 \text{ ms} \pm 56$ during control versus $323 \text{ ms} \pm 72$ under mexiletine, $p < 0.02$, Table 2). In cases 17 and 31 the tachycardia rate increased so that immediate DC cardioversion

became necessary. Such a high rate of ventricular tachycardia was not observed previously in these two patients; case 31, however, had experienced several syncopal attacks.

DISOPYRAMIDE

Disopyramide, 450 to 900 mg daily, was given to 25 patients. Four patients had spontaneous recurrences. Ventricular tachycardias were induced by single premature stimuli in nine patients and by double premature stimuli in eight. Atrial stimulation started the ventricular tachycardia in case 18 and the introduction of the electrode catheter into the right ventricle in case 33. Case 9 showed a repetitive ventricular response under the influence of disopyramide. Only in one case (case 23) was ventricular tachycardia in

Fig. 2 Comparison of the effect of mexiletine and disopyramide on the cycle length of sustained ventricular tachycardia in 21 patients. Whereas no significant difference can be measured under mexiletine, disopyramide prolongs the mean cycle length from $305 \text{ ms} \pm 36$ to $392 \text{ ms} \pm 74$ ($p < 0.01$). The mean cycle lengths under mexiletine and disopyramide differ, too ($p < 0.01$).

response to ventricular stimulation prevented by disopyramide. The cycle length of ventricular tachycardia increased from $301 \text{ ms} \pm 42$ to $387 \text{ ms} \pm 75$ ($p < 0.01$).

MEXILETINE AND DISOPYRAMIDE

A representative comparison of the effect of mexiletine and disopyramide on the rate of ventricular tachycardia is shown in Fig. 1. In this 50 year old patient (case 7) with congestive cardiomyopathy and a history of 50 sustained ventricular tachycardias, the cycle length of tachycardia was prolonged under mexiletine from 280 ms to 300 ms, and under disopyramide to 365 ms. In this way, the drug effects on the rate of tachycardia in the same person could be analysed in 21 patients (Fig. 2). The mean cycle length of ventricular tachycardia was unchanged by mexiletine ($305 \text{ ms} \pm 36$ during control versus $320 \text{ ms} \pm 62$ under drug influence). Under the influence of disopyramide, a prolongation of the mean cycle length from $305 \text{ ms} \pm 36$ to $392 \text{ ms} \pm 74$ was observed ($p < 0.01$). The difference between the cycle length of the ventricular tachycardia under mexiletine and under disopyramide was significant also ($p < 0.01$).

FOLLOW-UP

Seven patients were maintained on chronic oral

treatment with mexiletine for a mean of $26 \text{ months} \pm 5$. Two of the three patients, whose arrhythmias were suppressed during the electrophysiological study, did not experience persistent ventricular tachycardias again for 20 months (case 16) and 29 months (case 15).

In the third patient, mexiletine was discontinued because of a rise of liver enzymes. Though still inducible by double premature stimuli, persistent ventricular tachycardia did not return in one further patient for 24 months (case 12). On the other hand, three patients, still inducible, died suddenly: one in the hospital (case 25), one after three months (case 7), and the third after 25 months (case 8).

Twelve patients were chronically treated with disopyramide for $22 \text{ months} \pm 9$. The patient with total suppression of the ventricular tachycardia has been free from further attacks until now for 32 months (case 4). In case 9 with repetitive response, sustained tachycardias returned, were self-terminating, however, and less frequent. One further patient has also been free from ventricular tachycardias for 18 months so far (case 14). Recurrences of ventricular tachycardias were observed in eight patients but with a distinct reduction of frequency.

Documented recurrences of three of these patients showed a slow rate similar to the electrophysiologically induced ventricular tachycardia. Three patients died: one patient had three spontaneously terminating tachycardias and died suddenly 11 months later (case 11). One died because of pulmonary embolism after eight months; in the meantime, three spontaneously terminating tachycardias recurred (case 12). The third patient had no relapse until he died suddenly because of ventricular fibrillation after nine months (case 13).

ADVERSE EFFECTS

During mexiletine treatment, one patient complained about nausea that did not necessitate a change in treatment. Laboratory data of one patient indicated hepatic dysfunction so that treatment was discontinued though the rise of the liver enzymes could not be attributed with certainty to the drug. In the other patients, the drug was well tolerated. Disopyramide produced a pronounced negative inotropic effect in three patients; in one patient, low output failure occurred, which had to be controlled by catecholamine infusion. Two men experienced urinary retention. One patient reported dizziness.

Discussion

INDUCIBILITY

Complete suppression of sustained ventricular tachycardias by oral mexiletine or disopyramide during programmed stimulation could be accomplished

in a minority of our patients only. In other series, complete suppression was reached in eight of 12¹⁰ and in one of five⁵ by disopyramide, and in two out of 12 patients with sustained tachycardia by mexiletine¹¹; a somewhat higher dose of either compound was administered. Comparing these data with our results, an increase of dosage, especially of mexiletine, could have led to a slightly higher percentage of complete suppression.

A major reason for the low rate of complete suppression appears to be the highly selected group of patients with tachycardias previously resistant to several antiarrhythmic agents, as listed in Table 1. From our results, these patients, resistant in particular to other class I antiarrhythmic agents, respond rarely to mexiletine and disopyramide.

RATE OF VENTRICULAR TACHYCARDIA

The rate of ventricular tachycardias was not significantly influenced by mexiletine, as in previous studies.¹² In individual patients, a distinct increase of rate was observed. Similar observations have been reported under the influence of phenytoin and lignocaine.¹³ In contrast to mexiletine, disopyramide decreased considerably the rate of ventricular tachycardias. A similar decrease in the rate of ventricular tachycardia has been observed in individual patients.^{5 14} In the study of Benditt *et al.*¹⁰ and of Breithardt *et al.*¹² the decrease in the rate of tachycardia was not significant, however; this disparity might be because of the small sample size in these studies. If in a given patient complete suppression cannot be achieved, lowering the rate of the tachycardia—for example with disopyramide—is a major goal of treatment, so that the tachycardia is tolerated haemodynamically until medical assistance is available.

SPONTANEOUS RECURRENCES

Tentative conclusions only can be drawn from the follow-up of our patients, since a selected subgroup was maintained on chronic treatment. Patients with complete suppression showed an excellent prognosis even after a follow-up of two years. In the group of patients with tachycardias still inducible, most patients experienced recurrences, but less frequently and at a lower rate. On the other hand, one third of the patients died suddenly after a mean of two years. Whether the clinical course of such patients can be favourably influenced by alternative treatments such as other drugs or antiarrhythmic cardiac surgery is the subject of current investigations.

LIMITATIONS OF STUDY

The present investigation is a retrospective study, and the study groups are not identical. Therefore, conclu-

sions considering effectiveness and prognosis have to be drawn cautiously. For statistical analysis, however, only those patients were considered who were treated with either substance.

During programmed ventricular stimulation premature ventricular complexes, delivered by the stimulation unit, start the ventricular tachycardia. In this way, ventricular stimulation evaluates the ability of the re-entrant circuit to perpetuate ventricular tachycardia under the influence of antiarrhythmic drugs. The influence of antiarrhythmic drugs on the spontaneous ventricular complexes for initiation of tachycardias was not assessed.^{3 5}

Nevertheless, several previous studies have shown that programmed ventricular stimulation fairly predicted the clinical outcome, as in this report.^{3 14 15} Whether quantitative analysis of spontaneous ventricular arrhythmias in these special patients is of additional value for prediction of antiarrhythmic efficacy, needs further investigations.

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