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-
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. The electrode catheter thereafter was advanced to the apex of the right ventricle for ventricular 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 \( S_1 \) 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 \( S_2 \) 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

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Mexiletine</th>
<th>Disopyramide</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>Cycle length (ms)</td>
<td>Induction</td>
</tr>
<tr>
<td>1</td>
<td></td>
<td>Spontaneous</td>
</tr>
<tr>
<td>2</td>
<td>272</td>
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<tr>
<td>3</td>
<td>307</td>
<td>500 S, S, S, S</td>
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<tr>
<td>4</td>
<td>400</td>
<td>Atrial</td>
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<td>353</td>
<td>Atrial</td>
</tr>
<tr>
<td>6</td>
<td>413</td>
<td>Spontaneous</td>
</tr>
<tr>
<td>7</td>
<td>300</td>
<td>600 S, S, S</td>
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<tr>
<td>8</td>
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<td>600 S, S, S</td>
</tr>
<tr>
<td>9</td>
<td>428</td>
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<tr>
<td>10</td>
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<td>600 S, S, S</td>
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<td>11</td>
<td>375</td>
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<td>12</td>
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<td>Catheter</td>
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<tr>
<td>13</td>
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<td>Spontaneous</td>
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<td>15</td>
<td>300</td>
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<td>220</td>
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<tr>
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<td>333</td>
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<td>200</td>
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<td>355</td>
<td>600 S, S, S</td>
</tr>
<tr>
<td>21</td>
<td>250</td>
<td>600 S, S, S</td>
</tr>
</tbody>
</table>

Mean ± SD 320±62****

| Mean ± SD 392±74**** |

*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 I 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 electrophysiologic 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
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Results

MEXILETINE
Mexiteline, 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 ms ± 56 during control versus 323 ms ± 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
response to ventricular stimulation prevented by disopyramide. The cycle length of ventricular tachycardia increased from 301 ms±42 to 387 ms±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 ms±36 during control versus 320 ms±62 under drug influence). Under the influence of disopyramide, a prolongation of the mean cycle length from 305 ms±36 to 392 ms±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 months±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 months±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...
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in a minority of our patients only. In other series, complete suppression was reached in eight of 12\(^6\) and in one of five\(^5\) by disopyramide, and in two out of 12 patients with sustained tachycardia by mexiletine\(^11\); 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 \textit{et al.}\(^10\) and of Breithardt \textit{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, conclusions 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.

References


Requests for reprints to Dr M Manz, Medizinische Universitätsklinik, Bonn, Innere Medizin-Kardiologie, Sigmund Freud Str. 25, D-5300 Bonn, West Germany.
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