Antiarhythmic Effects of Selective Prolongation of Refractoriness

Electrophysiologic Actions of Sematilide HCl in Humans

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Background. Recent data have suggested that antiarrhythmic agents that act largely by delaying conduction may not be as effective in controlling ventricular arrhythmias as those that prolong repolarization. Recently, numerous “pure” class III agents have been developed.

Methods and Results. The antiarrhythmic and electrophysiologic profiles of sematilide, a “pure” class III agent, were determined in 27 patients with clinical ventricular arrhythmias and inducible sustained ventricular tachycardia during electrophysiologic study. After treatment with oral sematilide (mean dose, 133±29 mg every 8 hours), the patients underwent repeat 24-hour ambulatory ECG monitoring and electrophysiologic study. The baseline sinus cycle length and QT, QTc, JT, and JT, intervals were significantly increased 8 to 17% by sematilide (P=.001 to .029). There were no changes in the PR or QRS intervals. Sematilide (at a paced cycle length of 600 ms) significantly increased the atrial effective refractory period (238±32 to 264±32 ms; 11±16% increase from baseline; P=.013), atrioventricular nodal effective refractory period (296±74 to 354±71 ms; 20±19%; P=.029), and right ventricular effective refractory period (252±25 to 281±30 ms; 12±8%; P=.01) but did not significantly change the PA or HV intervals, the corrected sinus node recovery time, or the Wenckebach cycle length. Determination of the frequency-dependent effects of sematilide (n=10) on the right ventricular monophasic action potential duration (APDw) during ventricular pacing at cycle lengths of 600 to 300 ms revealed that the APDw was significantly prolonged by sematilide during ventricular pacing at 600 to 350 ms (APDw increase of 40±17, 27±21, 18±18, and 14±15 ms, respectively) but not at 300 ms (APDw increase of 13±19 ms). Sematilide significantly prolonged the APDw to a greater degree at longer than shorter cycle lengths (P=.02). The ventricular effective refractory period had a similar reverse frequency-dependent relation as the APDw. Sematilide had no effect on the ventricular effective refractory period-to-APDw ratio or on ventricular conduction. Sematilide suppressed the induction of sustained ventricular tachycardia in 41% of all patients exposed to sematilide. Prolongation of ventricular refractoriness was correlated with ventricular tachycardia suppression. The right ventricular effective refractory period (at 600 ms) increased by 38±14 ms in patients whose sustained ventricular tachycardia was suppressed by sematilide and by 19±18 ms in patients not suppressed (P=.015). One patient developed short runs of pause-dependent nonsustained ventricular tachycardia. Eight patients were placed on long-term sematilide therapy, and during a mean follow-up period of 7.0±7.5 months, two patients developed sudden cardiac death, and one additional patient had recurrent sustained ventricular tachycardia.

Conclusions. The electrophysiologic profile of sematilide is consistent with selective block of outward potassium currents and associated isolated lengthening of the ventricular effective refractory period and APD; sematilide demonstrates a significant degree of reverse frequency-dependence of the ventricular APD and effective refractory period; and suppression of ventricular tachycardia inducibility by sematilide appears to be correlated with increases in the right ventricular effective refractory period. (Circulation. 1993;88:1072-1082.)

Key Words • ventricular tachycardia • electrophysiologic study • arrhythmias

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In controlling life-threatening ventricular arrhythmias by pharmacological means, two major approaches, namely, slowing conduction (class I effects) and delaying repolarization (class III effects), have been used widely.1-3 Conduction slowing is usually achieved by inhibiting the fast inward sodium current. Prolongation of refractoriness may be obtained by inhibition of outward currents or increasing inward currents or by delaying the recovery of sodium channels during phase 3 of the action potential.4,5 In the case of many conventional antiarrhythmic compounds, there is an overlap between these fundamental electrophysiologic properties.6-10 The negative results of the Cardiac Arrhythmia Suppression Trial using class Ic agents11,12 and the high efficacy associated with amiodarone13-15 have resulted in marked interest in controlling ventricular arrhythmias...
by class III actions. However, neither of the two available oral class III agents—amiodarone and sotalol—solely prolongs refractoriness without exerting other pharmacologic effects. Amiodarone prolongs the action potential duration (APD) but also slows fast sodium channel–mediated conduction and has non-competitive antiadrenergic actions and calcium channel–blocking effects, whereas sotalol is a noneffective β-blocker. The question has therefore arisen whether “pure” or isolated prolongation of myocardial refractoriness may provide a new, simpler, and more specific treatment of cardiac arrhythmias.

Sematilide hydrochloride (Berlex Laboratories, Wayne, NJ) is a recently synthesized methysulfonyl-amino parasubstituted analogue of procainamide that has been shown to have class III activity in isolated cardiac tissues and intact animals. It has been demonstrated to be a blocker of the delayed rectifying potassium current (IK) and preliminary in vitro studies suggest that IK block is voltage independent. In addition, sematilide is devoid of effects on sodium channels and has no autonomic interactions and is effective in controlling experimental ventricular arrhythmias in animal studies. However, its electrophysiologic profile has not been established in humans.

The purpose of this prospective investigation was to define the electrophysiologic profile, arrhythmic efficacy during electrophysiologic study, and safety of sematilide HCl when evaluated in patients with sustained ventricular tachycardia, ventricular fibrillation, or syncpe secondary to ventricular tachycardia.

Methods

Patient Population

Patients were considered for entry into the study if they had (1) ventricular tachycardia, ventricular fibrillation, aborted sudden death, or syncpe secondary to ventricular tachyarrhythmias; and (2) inducible sustained monomorphic ventricular tachycardia or, in patients with clinical cardiac arrest or ventricular fibrillation, inducible sustained polymorphic ventricular tachycardia or ventricular fibrillation during baseline drug-free electrophysiologic study. Exclusion criteria were unstable angina, myocardial infarction within 1 month or a sustained ventricular tachyarrhythmia occurring only in the setting of an acute myocardial infarction, class IV congestive heart failure or left ventricular ejection fraction of less than 0.20, creatinine clearance less than 55 mL/min, second- or third-degree atrioventricular block or severe symptomatic sinus node dysfunction, amiodarone therapy within the previous 3 months, or baseline QTc of more than 450 ms.

Study Protocol

Patients were admitted to a telemetry ward with continuous ECG monitoring, and all antiarrhythmic agents, including β-blockers, were discontinued for at least five half-lives for these agents. Twenty-four-hour ECG ambulatory monitoring was performed on the day before each electrophysiologic study. This investigation was approved by the West Los Angeles VA Medical Center Human Investigation Committee. All patients gave written informed consent.

Patients with inducible sustained ventricular tachyarrhythmias (see below) during baseline electrophysiologic study underwent serial electropharmacological testing. Sematilide was the first pharmacological agent evaluated by electrophysiologic study in 21 patients and the second drug in the remaining six patients. The initial dose of sematilide HCl in the first 3 patients was 75 mg orally every 8 hours, and the remaining 24 patients were started on 100 mg orally every 8 hours. After six doses of 75 to 100 mg, the sematilide dose was increased to 125 to 150 mg orally every 8 hours, and a repeat electrophysiologic study was performed after steady state was achieved (more than 48 hours; the elimination half-life is approximately 8 hours). Patients with creatinine clearance of more than 70 mL/min were increased to 200 mg every 8 hours if they had inducible ventricular tachycardia on the lower dose. Sematilide was discontinued if the QT interval increased to 550 ms or more than 25% of baseline, patients had a fivefold increase in nonsustained ventricular tachycardia runs, or new sustained ventricular tachycardia, ventricular fibrillation, or torsade de pointes developed and was thought to be secondary to drug-induced effect.

Electrophysiologic Study

Electrophysiologic study was performed in the baseline drug-free preabsorptive state 6 to 8 hours after the last dose of steady-state sematilide dosing. Two quadrupolar 6F catheters (5-mm spacing; USCI, Billerica, Mass) were placed via a femoral vein in the high right atrium and across the tricuspid valve to measure the His bundle electromgram. In addition, either a quadrupolar catheter or a 7F catheter with two platinum ring electrodes for pacing (located 2 mm from the tip) and a pair of Ag-AgCl electrodes (at the distal tip and 5 mm proximal from the tip) (EP Technology, Palo Alto, Calif) for recording of the right ventricular monophasic action potential were placed at the right ventricular apex. This catheter allows determination of both the ventricular effective refractory period and the monophasic action potential at the same location.

Pacing Protocol

All pacing was performed at twice the diastolic threshold and a pulse width of 2 ms using a programmable stimulator (Bloom Inc, Reading, Pa). Sinus node recovery time was determined following continuous atrial pacing at increasing rates for more than 1 minute. Atrial and atrioventricular nodal effective refractory periods were determined using a basic drive stimuli of 8 beats and applying an extrastimulus late in diastole and successively decrementing the coupling interval of the extrastimulus by 10 ms. The effective refractory period was reached when the extrastimulus failed to evoke a response on two successive attempts. The atrioventricular nodal effective refractory period could not be obtained in many patients because the atrial effective refractory period was longer than the atrioventricular nodal effective refractory period or atrioventricular Wenckebach occurred at the cycle lengths tested. In addition, three patients were in atrial fibrillation. The right ventricular effective refractory period was determined in a similar fashion as the atrial effective refractory period. The coupling interval of the extrastimulus was successively decreased by 5 ms in the patients in
whom monophasic action potentials were recorded and the drive train was increased to 14 beats.

**Right Ventricular Monophasic Action Potential Recordings and Measurements**

In the last 11 patients enrolled in this study, the frequency-dependent effects of sematilide on the monophasic action potential duration, ventricular effective refractory period, and QRS duration were attempted. However, in one patient, satisfactory baseline monophasic action potential recordings could not be obtained, and therefore frequency-dependent determinations were made in 10 patients. Right ventricular monophasic action potentials were recorded at paper speeds of 100 mm/s (MIDAS or VR16, PPG Inc, Lenexa, Kan) using the Ag-AgCl catheter in patients at both baseline and on maximum doses of sematilide. These recordings were made during steady-state right ventricular pacing at cycle lengths of 600, 500, 400, 350, and 300 ms for 150 to 200 complexes at twice-diastolic threshold. This was feasible in 8 patients at a cycle length of 600 ms and in all 10 patients at the other cycle lengths. The catheter position was recorded during the baseline electrophysiologic study and placed in the same position during subsequent electrophysiologic testing on sematilide.

The amplitude of the monophasic action potential was determined from the diastolic baseline to the plateau and the APD90 from the initial monophasic action potential upstroke to the point when repolarization was 90% complete. Monophasic action potential recordings of less than 8 mV were excluded. The APD90 was measured manually by two investigators who were blinded to the patients’ therapy. Interobserver variability was less than 5%.

**Ventricular Tachycardia Induction**

Attempts were made to induce ventricular tachycardia as previously described.33 Briefly, one, two, and three premature extrastimuli (at twice-diastolic threshold) were delivered during paced ventricular cycle lengths of 500 and 400 ms. All premature extrastimuli were brought to refractoriness, and premature ventricular stimulation was performed at both the ventricular apex and the right ventricular outflow tract. During the baseline electrophysiologic study, sustained ventricular arrhythmias not requiring cardioversion were induced twice to demonstrate reproducibility. Premature ventricular stimulation (using the same protocol as at baseline) during sematilide therapy was concluded if a sustained ventricular arrhythmia was induced.

**Definitions**

Sustained ventricular tachycardia had a rate of more than 100 beats per minute and lasted at least 30 seconds or required intervention for termination because of hemodynamic compromise. The morphology of induced ventricular tachycardia was defined as monomorphic and polymorphic using previously described criteria.34 Ventricular fibrillation was defined as a tachycardia with irregular cycle lengths and constantly changing surface QRS morphology at a mean cycle length of less than 200 ms.

In response to pharmacological therapy, responders had 15 or less beats of inducible nonsustained ventricular tachycardia induced during electropharmacologic study. Partial responders had more than 15 beats of nonsustained ventricular tachycardia induced that stopped spontaneously within 30 seconds and did not cause hemodynamic symptoms. Nonresponders had persistent inducible sustained ventricular tachycardia. The differentiation of patients into responders, partial responders, and nonresponders was based solely on the results of invasive electropharmacologic study and not on ambulatory monitoring.

**Outpatient Therapy**

Responders and a subgroup of partial responders were enrolled in long-term outpatient therapy with sematilide and were followed in the outpatient arrhythmia clinic at 2 weeks, 6 weeks, 3 months, and every 3 months thereafter.

**ECG Analysis**

The morning resting surface ECG was evaluated for changes in PR, QRS, QT, QTc, and JTc intervals. The QT interval was corrected using Bazett’s formula,35 and the JTc interval was defined as (JT)/(RR)1/2. Twenty-four-hour ambulatory ECG monitoring tapes were analyzed commercially (Cardio Data, Haddonfield, NJ) for premature ventricular complexes per 24 hours and the frequency of pairs and ventricular tachycardia runs during the recording period.

**Left Ventricular Ejection Fraction**

The left ventricular ejection fraction was determined using either two-dimensional echocardiography (n=18) or contrast left ventriculography (n=9).

**Patient Follow-up**

Follow-up was obtained by telephone interview with the patient or through the attending physician if the patient died or had an arrhythmic event. Sudden death was defined as death that occurred within 1 hour of the onset of symptoms and was unexpected.

**Data Analysis**

For patients who received multiple dose levels of sematilide, data are given for the maximum clinically tolerated dose. P values for comparisons in Tables 1 through 4 are from either Fisher’s exact test or Pearson’s χ² test for frequency data or Student’s paired t test (two-tailed) for mean values, unless otherwise stated. However, more comprehensive analyses were performed when multiple pacings were used. The changes

<table>
<thead>
<tr>
<th>TABLE 1.</th>
<th>ECG Effects at Baseline and With Sematilide</th>
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</thead>
<tbody>
<tr>
<td>Interval</td>
<td>Baseline</td>
</tr>
<tr>
<td>RR</td>
<td>866±128</td>
</tr>
<tr>
<td>PR</td>
<td>189±43</td>
</tr>
<tr>
<td>QRS</td>
<td>110±32</td>
</tr>
<tr>
<td>QT</td>
<td>396±43</td>
</tr>
<tr>
<td>QTc</td>
<td>429±33</td>
</tr>
<tr>
<td>JT</td>
<td>287±41</td>
</tr>
<tr>
<td>JTc</td>
<td>318±33</td>
</tr>
</tbody>
</table>

n=27 except for RR and PR intervals, where n=24 (three patients were in atrial fibrillation). All measurements are given in ms.
in the APD_{90} ventricular effective refractory period, QRS duration, and ventricular effective refractory period–APD_{90} ratio after sematilide, and the consistency of these changes compared with baseline measurements as a function of cycle length were determined using repeated-measures ANOVA with the Greenhouse-Geisser correction within-subject correlation. Post hoc paired t tests were performed at each paced cycle length and are reported in the text. No formal correction was made for multiple comparisons. To apply the Bonferroni correction, a statistically significant value equals .05 divided by the number of comparisons. Thus, because the frequency-dependent electrophysiologic effects were determined at five paced cycle lengths, a value of \( P \leq .01 \) would be considered significant at an individual paced cycle length using the Bonferroni correction.

Data are expressed as mean±SD values except for the figures, in which data are expressed as mean±SEM values. Significance was defined as \( P \leq .05 \). Values of \( P \leq .30 \) are given in the text, and \( P > .30 \) values are listed as nonsignificant (NS).

Results

Patient Population

Twenty-seven patients were enrolled in this study. All were men, and mean age was 58±10 years. The presenting arrhythmias included sustained ventricular tachycardia in 13 patients and out-of-hospital cardiac arrest in 2. The remaining 12 had syncope; the maximum clinical arrhythmia in these patients was nonsustained ventricular tachycardia (10 patients) and frequent premature ventricular complexes (1 patient). The cardiac diagnoses included a history of myocardial infarction (17 patients), idiopathic dilated cardiomyopathy (5 patients), valvular heart disease (2 patients), coronary artery disease (1 patient), hypertensive heart disease (1 patient), and no known structural heart disease (1 patient). Mean left ventricular ejection fraction was 0.35±0.12 (range, 0.20 to 0.68). The patients had been previously treated with a median of 1.6 (range, 0 to 7) antiarrhythmic agents before entry into this study. Sematilide was the first drug tested during electrophysiologic studies in 21 patients and the second drug tested in the remaining 6 patients.

The maximum doses of sematilide (every 8 hours) evaluated or clinically tolerated were 75 mg (1 patient), 100 mg (8 patients), 125 mg (1 patient), 150 mg (16 patients), and 200 mg (1 patient). The mean dose of sematilide was 133±29 mg every 8 hours.

ECG Effects

Sinus rates and PR intervals could not be evaluated in three patients because of atrial fibrillation (Table 1). Sematilide significantly increased the sinus cycle length by 8% and the QT, QTc, JT, and JTc intervals by 8% to 17%. There was no significant effect on PR or QRS intervals.

Twenty-four-Hour Ambulatory Monitoring Effects

Twenty-one patients had paired 24-hour ambulatory monitoring at drug-free baseline and on the dose of sematilide tested at electrophysiologic study (Table 2). The absolute number of premature ventricular complexes per 24 hours was decreased by 58% during sematilide administration (\( P=0.003 \)). Only 5 of 21 patients (24%) with paired recordings had their premature ventricular complexes suppressed by 80% or more. There also was a significant reduction after sematilide in runs of nonsustained ventricular tachycardia and nonsignificant trends for reductions in ventricular couplets and slowing of nonsustained ventricular tachycardia in patients who had these arrhythmias on their baseline monitoring.

Electrophysiologic Effects

All patients had baseline electrophysiologic studies, and 25 of the 27 patients underwent electrophysiologic study while on sematilide (Table 3). One patient developed apparent proarrhythmia (described below), and another patient (described below) had excessive QT prolongation (as defined by our protocol); thus, sematilide was discontinued before electropharmacological study in these 2 patients (see adverse events).

During the electrophysiologic study, sematilide did not significantly affect the corrected sinus node recovery time, Wenckebach cycle length, or PA or HV intervals. The AH interval increased by 37% at a paced cycle length of 500 ms but was not significantly prolonged at the other cycle lengths tested (\( P=0.14 \) to .21). The atrial effective refractory period increased by 11% (\( P=0.013 \)) at a paced atrial cycle length of 600 ms but was not significantly increased at cycle lengths of 500 or 400 ms (\( P=NS \) and .054, respectively). In the relatively small number of patients examined (\( n=7 \) or 8), sematilide prolonged the atrioventricular node effective refractory period by 20 to 22%. The right ventricular apex effective refractory period was prolonged by 11 to 13% (\( P<0.001 \)).

Frequency-Dependent Effects of Sematilide on APD_{90}, QRS Duration, and Ventricular Effective Refractory Period

As the ventricular pacing cycle length was decreased from 600 to 300 ms, the APD_{90} at baseline and after sematilide shortened (\( n=10 \), Fig 1). Compared with baseline, sematilide increased the mean APD_{90} by 40±17 ms (\( P<0.001 \); paired t test; 15.4% increase from baseline), 27±21 ms (\( P=0.003 \); 10.6%), 18±18 ms

Table 2. Twenty-Four-Hour Ambulatory Monitoring Effects

<table>
<thead>
<tr>
<th>Effect</th>
<th>n</th>
<th>Baseline</th>
<th>Sematilide</th>
<th>( P )</th>
</tr>
</thead>
<tbody>
<tr>
<td>PVCs per 24 hours</td>
<td>21</td>
<td>2751±2482</td>
<td>1168±1129</td>
<td>.003</td>
</tr>
<tr>
<td>Couplets per 24 hours</td>
<td>17</td>
<td>332±492</td>
<td>84±206</td>
<td>.065</td>
</tr>
<tr>
<td>NSVT runs per 24 hours</td>
<td>13</td>
<td>11±12</td>
<td>3±8</td>
<td>.033</td>
</tr>
<tr>
<td>Fastest NSVT (ms)</td>
<td>6</td>
<td>390±84</td>
<td>500±217</td>
<td>.079</td>
</tr>
<tr>
<td>Longest NSVT (beats)</td>
<td>6</td>
<td>15.8±20.7</td>
<td>4.5±4</td>
<td>.25</td>
</tr>
</tbody>
</table>

NSVT indicates nonsustained ventricular tachycardia.
Table 3. Electrophysiologic Effects at Baseline and With Sematilide

<table>
<thead>
<tr>
<th></th>
<th>n</th>
<th>Baseline</th>
<th>Sematilide</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sinus CL</td>
<td>22</td>
<td>840±178</td>
<td>881±144</td>
<td>.074</td>
</tr>
<tr>
<td>PA sinus</td>
<td>19</td>
<td>39±12</td>
<td>36±14</td>
<td>NS</td>
</tr>
<tr>
<td>PA (600 ms)</td>
<td>10</td>
<td>48±11</td>
<td>45±17</td>
<td>NS</td>
</tr>
<tr>
<td>PA (500 ms)</td>
<td>12</td>
<td>50±11</td>
<td>46±17</td>
<td>NS</td>
</tr>
<tr>
<td>PA (400 ms)</td>
<td>8</td>
<td>44±13</td>
<td>41±20</td>
<td>NS</td>
</tr>
<tr>
<td>Wenckebach CL</td>
<td>18</td>
<td>429±120</td>
<td>438±86</td>
<td>NS</td>
</tr>
<tr>
<td>CSNRT</td>
<td>17</td>
<td>290±202</td>
<td>271±182</td>
<td>NS</td>
</tr>
<tr>
<td>AH sinus</td>
<td>22</td>
<td>96±21</td>
<td>104±31</td>
<td>.21</td>
</tr>
<tr>
<td>AH (600 ms)</td>
<td>11</td>
<td>114±27</td>
<td>125±38</td>
<td>.14</td>
</tr>
<tr>
<td>AH (500 ms)</td>
<td>12</td>
<td>118±26</td>
<td>162±60</td>
<td>.018</td>
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<td>HV sinus</td>
<td>21</td>
<td>64±13</td>
<td>63±11</td>
<td>NS</td>
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<td>HV (600 ms)</td>
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<td>60±14</td>
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<td>NS</td>
</tr>
<tr>
<td>HV (400 ms)</td>
<td>9</td>
<td>62±13</td>
<td>64±12</td>
<td>NS</td>
</tr>
<tr>
<td>Atrial ERP (600 ms)</td>
<td>14</td>
<td>238±32</td>
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<td>.013</td>
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<tr>
<td>Atrial ERP (500 ms)</td>
<td>14</td>
<td>234±30</td>
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<td>NS</td>
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<tr>
<td>Atrial ERP (400 ms)</td>
<td>12</td>
<td>208±43</td>
<td>235±19</td>
<td>.054</td>
</tr>
<tr>
<td>Atrioventricular nodal ERP (600 ms)</td>
<td>7</td>
<td>296±74</td>
<td>354±71</td>
<td>.029</td>
</tr>
<tr>
<td>Atrioventricular nodal ERP (500 ms)</td>
<td>8</td>
<td>284±74</td>
<td>347±60</td>
<td>.022</td>
</tr>
<tr>
<td>VERP (600 ms)</td>
<td>19</td>
<td>252±25</td>
<td>281±30</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>VERP (500 ms)</td>
<td>24</td>
<td>241±24</td>
<td>269±25</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>VERP (400 ms)</td>
<td>25</td>
<td>231±24</td>
<td>255±21</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

CL indicates cycle length; CSNRT, sinus node recovery time; VERP, ventricular effective refractory period. All measurements are given in ms.

Sematilide increased the APD₀ in a reverse frequency-dependent manner. After sematilide administration, the increase in APD₀ was significantly greater compared with baseline at longer than at shorter paced cycle lengths (eg, P<.009 for APD₀ prolongation by sematilide at 600 ms compared with 300 ms). The reverse frequency-dependent effect of sematilide on repolarization was confirmed by demonstrating a significant interaction between APD₀ prolongation and the paced cycle length using repeated-measures ANOVA (P≤.02).

The increase in the APD₀ was also analyzed as a function of the baseline diastolic interval (ie, the paced cycle length minus the baseline APD₀) using linear regression. There was a significant correlation for both the magnitude of sematilide-induced APD₀ prolongation (r=.55, P<.001) and the percent increase in the APD₀ (r=.45, P=.001) versus diastolic interval, indicating less prolongation of the APD₀ by sematilide at shorter than at longer diastolic intervals.

Compared with baseline, the changes in the ventricular effective refractory period after sematilide paralleled those of the APD₀ (Fig 1). Sematilide significantly increased the ventricular effective refractory period (versus baseline) by 21±19 ms (P=.015; paired t test; 8.8%), 25±18 ms (P=.004; 11.1%), 15±15 ms (P=.004; 6.9%), 18±17 ms (P=.006; 8.7%), and 13±12 ms (P=.008; 6.6%) at paced cycle lengths of 600, 500, 400, 350, and 300 ms, respectively. Sematilide-induced prolongation of the ventricular effective refractory period was greater at longer than at shorter paced cycle lengths (repeated-measures ANOVA, P<.05).

There were no changes in the QRS duration at baseline or after sematilide at any paced cycle length (Fig 2). Similarly, sematilide had no effect on the ventricular effective refractory period-to-APD₀ ratio compared with baseline (Fig 2).

Ventricular Tachycardia Induction

At baseline, sustained monomorphic ventricular tachycardia was induced in 26 patients, and sustained polymorphic ventricular tachycardia was induced in 1 patient who had a history of out-of-hospital cardiac arrest. As discussed above, 2 patients did not undergo electrophysiologic study while taking sematilide.

After sematilide administration, 7 patients (26% of all study patients; 28% of those undergoing electrophysio-
logic study on sematilide) were full responders, and 4 additional patients (15% of all study patients; 16% of patients undergoing electrophysiologic study on sematilide) were partial responders. Thus, the total number of responders and partial responders was 11 (41% of all study patients; 44% of all patients undergoing electrophysiologic study on sematilide). In patients who continued to have inducible ventricular tachycardia while on sematilide, the mean ventricular tachycardia cycle length increased from 249±53 ms at baseline to 269±43 ms (8% increase, 
\( P = 0.042 \)) after sematilide. Sustained ventricular tachycardia was induced by 2.6±0.5 premature ventricular stimuli at baseline and 2.8±0.4 (\( P = \text{NS} \)) after sematilide.

Nonresponders Compared With Responders

When the 11 responders and partial responders were compared with the 14 nonresponders, there were no differences in clinical parameters, left ventricular dimensions, left ventricular ejection fraction, and the dose of sematilide tested in responders (130±37 mg every 8 hours) and nonresponders (141±19 mg every 8 hours, \( P = \text{NS} \)) (Table 4). In addition, QT duration (\( P = \text{NS} \) by repeated-measures ANOVA), baseline ventricular ectopy, the suppression of ventricular ectopy (\( P = \text{NS} \) by Wilcoxon rank-sum test), the ventricular effective refractory period at baseline or during sematilide (\( P = \text{NS} \) by repeated-measures ANOVA), and the induced ventricular tachycardia cycle length were similar in the two groups. The suppression of ventricular tachycardia inducibility in responders was correlated with prolongation of refractoriness. The increase in the right ventricular effective refractory period during sematilide compared with baseline was 100 to 147% greater (\( P = 0.003 \) to .015) depending on the cycle length in responders than in nonresponders (overall \( P = 0.03 \) by repeated-measures ANOVA). Six responders (55%) but none of the nonresponders had an increase in ventricular effective refractory period at a paced cycle length of 400 ms of more than 30 ms (\( P = 0.003 \)). Although prolongation of the right ventricular effective refractory period was correlated with suppression of inducibility of ventricular tachycardia, no mechanism has been proven since unmeasured factors (eg, blood sematilide levels) may have played an important role.

Adverse Effects

Two patients developed a protocol-defined adverse effect at the first dose level (100 mg every 8 hours) tested. One patient had QT prolongation from 410 to 520 ms without any evidence of clinical proarrhythmia. The other patient developed frequent runs of pause-dependent asymptomatic nonsustained ventricular tachycardia of 5 to 7 beats in duration. His QT interval was prolonged more than 25% from 410 to 520 ms. Sematilide was stopped, and the arrhythmia resolved without further therapy. Two other patients developed nausea (one also had dizziness and distal upper extremity decreased sensation bilaterally) after an increase to a higher dose level (150 and 200 mg in each patient), whereas another patient developed asymptomatic QT prolongation (QT=560 ms without proarrhythmia) after sematilide was increased to 200 mg every 8 hours. No patients developed new congestive heart failure or worsening of preexisting congestive heart failure during the inpatient phase.

Outcome on Oral Therapy

Eight of the 25 patients who underwent electrophysiologic study while on sematilide were discharged on the medication. During a mean follow-up period of 7.0±7.5 months of sematilide therapy, 2 patients taking sematilide died of presumed tachyarhythmic causes, and another patient developed recurrent sustained ventricular tachycardia after 17 months of sematilide therapy (all were full responders). The latter patient, although successfully resuscitated, died 10 hours after hospital admission from bradyarrhythmic electromechanical dissociation. An autopsy was not performed, and a myocardial infarction was not definitively excluded. One of the other patients who died had a left ventricular ejection fraction of 0.25 and history of syncope. He was unexpectedly found dead at home after 2 weeks of sematilide therapy, and his death was attributed to arrhythmia recurrence. The other patient had valvular heart disease and congestive heart failure. A 24-hour ambulatory ECG performed 2 days before his death revealed very frequent (41 runs per hour) 3-22 beat runs of monomorphic nonsustained ventricular tachycardia. While in the emergency department with pulmonary edema, he developed a witnessed episode of sustained ventricular tachycardia and was promptly cardioverted to asystole. Resuscitative effects were unsuccessful. Thus, it is uncertain whether the patient had primary proarrhythmia causing his congestive heart failure to worsen and his eventual death or if the frequent ventricular ectopy was the result of decompensated congestive heart failure. There were no other episodes of ventricular tachycardia recurrence, syncope, or nonsudden death in the patients receiving sematilide.

Nineteen patients followed for 16.8±7.3 months were not treated chronically with sematilide: 11 received amiodarone, 4 were treated with an implantable cardioverter-defibrillator, 1 no longer had inducible sustained ventricular tachycardia after coronary artery bypass grafting and was not treated with antiarrhythmic therapy, and 3 patients were treated with procainamide or quinidine. During follow-up, 2 patients died suddenly, 1 died of congestive heart failure, 1 patient had recurrent sustained ventricular tachycardia, and 3 patients had appropriate implantable cardioverter-defibrillator discharges. Another patient, whose sematilide was discontinued at the discretion of his attending physician, was placed on amiodarone and died suddenly 4 weeks later.
TABLE 4. Predictors of Suppression of Inducible Sustained Ventricular Tachycardia

<table>
<thead>
<tr>
<th>Predictor</th>
<th>Partial and full responders</th>
<th>Nonresponders</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>11 (44%)</td>
<td>14 (56%)</td>
<td>NS</td>
</tr>
<tr>
<td>Age (y)</td>
<td>59±14</td>
<td>57±7</td>
<td>NS</td>
</tr>
<tr>
<td>History of sustained ventricular tachycardia and/or ventricular fibrillation</td>
<td>5</td>
<td>9</td>
<td>NS</td>
</tr>
<tr>
<td>History of myocardial infarction</td>
<td>6</td>
<td>9</td>
<td>NS</td>
</tr>
<tr>
<td>Congestive cardiomyopathy</td>
<td>1</td>
<td>3</td>
<td>NS</td>
</tr>
<tr>
<td>Sematilide every 8 hours (mg)</td>
<td>130±37</td>
<td>141±19</td>
<td>NS</td>
</tr>
<tr>
<td>LVEF (%)</td>
<td>36±12</td>
<td>31±8</td>
<td>.23</td>
</tr>
<tr>
<td>LVEDD (mm)</td>
<td>64±21</td>
<td>65±7</td>
<td>NS</td>
</tr>
<tr>
<td>LVESD (mm)</td>
<td>46±14</td>
<td>50±8</td>
<td>NS</td>
</tr>
<tr>
<td>Baseline QT</td>
<td>413±46</td>
<td>382±40</td>
<td>.083</td>
</tr>
<tr>
<td>Sematilide QT</td>
<td>433±52</td>
<td>441±53</td>
<td>NS</td>
</tr>
<tr>
<td>Change in QT</td>
<td>21±65</td>
<td>39±30</td>
<td>.09</td>
</tr>
</tbody>
</table>
| Baseline QTₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙ°
| PVC reduction                                       | 242±52                      | 240±51        | NS   |
| Median                                              | 52%                         | 55%           | NS   |
| 25th to 75th Percentile                             | 4% to 70%                   | −59% to 81%   |      |
| Baseline VERP (600 ms)                              | 246±29                      | 257±19        | NS   |
| VERP (500 ms)                                       | 235±29                      | 246±19        | .26  |
| VERP (400 ms)                                       | 225±25                      | 236±22        | .23  |
| Sematilide VERP (600 ms)                            | 287±29                      | 272±28        | .21  |
| VERP (500 ms)                                       | 274±27                      | 262±24        | .29  |
| VERP (400 ms)                                       | 261±22                      | 251±20        | .22  |
| Increase in VERP paced cycle length                 |                             |               |      |
| 600 ms                                              | 38±14                       | 19±18         | .015 |
| 500 ms                                              | 39±17                       | 19±14         | .006 |
| 400 ms                                              | 37±18                       | 15±15         | .003 |

LVEF indicates left ventricular ejection fraction; LVEDD, left ventricular end-diastolic dimension; LVESD, left ventricular end-systolic dimension; PVC, premature ventricular contraction; and VERP, ventricular effective refractory period. All electrophysiologic measurements are in ms except for the corrected QTₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙₙ°

Discussion

Electrophysiologic Profile

This study demonstrates that in humans, sematilide exerts selective class III effects in the ventricle. It significantly prolonged the ventricular effective refractory period and APD₉₀ without exerting any demonstrable sodium channel-blocking effects. Sematilide did not alter ventricular conduction time as measured by QRS duration, HV interval, or ventricular effective refractory period-to-APD₉₀ ratio. The lack of a change in the ventricular effective refractory period-to-APD₉₀ ratio by sematilide indicates that sematilide-induced prolongation of refractoriness is secondary to prolongation of the APD and not to delay in recovery of sodium channels independent of the APD changes. Thus, the overall electrophysiologic findings in humans are in accord with the results of in vitro and in vivo animal studies, indicating that the dominant and selective effect is on cardiac repolarization.

Sematilide slowed the sinus rate, increased the atrioventricular nodal effective refractory period, and tended to prolong the atrial effective refractory period. These findings suggest that the drug might lengthen APD in the human sinoatrial and atrioventricular nodes and in the atria. This is supported by data in isolated rabbit sinoatrial nodal tissue. These effects suggest that the drug may be useful in certain supraventricular arrhythmias and is likely to exert antifibrillatory actions in atrial fibrillation. The focus of this study, however, was on ventricular arrhythmias.

Frequency-Dependent Effects

Hondeghem and Schniders recently pointed out the opposite frequency-dependent effects of class I agents on the maximum rate of depolarization (Vₘₐₓ) and of
class III agents on myocardial repolarization. Although in the case of sodium channel blockers, the effect on $V_{\text{max}}$ is augmented as the stimulation frequency increases,$^{8,39}$ the degree of lengthening of the action potential duration by class III agents (eg, sotalol),$^{40,41}$ n-acetylcysteine$^{38}$ decreases at increasing pacing rates. This attenuation of drug-induced APD prolongation during short cycle lengths has been termed reverse frequency-dependence.$^{38,42}$ The reverse frequency-dependence of many class III agents may be secondary to (1) preferential drug binding to outward current potassium channels in the resting state with less binding during short cycle lengths because of the shortened diastolic interval. This is unlikely given the increasing data that $I_{\text{K}}$ blockers bind to the open channel and that $I_{\text{K}}$ block is frequency-dependent.$^{22,43-46}$ The reverse frequency-dependence may also be secondary to (2) extracellular potassium accumulation at short cycle lengths that increases the conductance of other potassium currents (eg, the inward rectifier, $I_{\text{K}}$)$^{47,48}$; (3) drug block of multiple channels with varying effects at long and short cycle lengths; and (4) block of the rapidly activating component of the delayed rectifier ($I_{\text{K}}$) with incomplete deactivation of the slowly activating component of $I_{\text{K}}$ ($I_{\text{K}}$) at rapid rates with subsequent increased outward currents.$^{49}$ Such a reverse frequency-dependent effect on repolarization was exhibited by sematilide in our study. The drug increased the APD and ventricular effective refractory period to the greatest degree during slow ventricular pacing (cycle lengths of 500 to 600 ms), and such increases were significantly attenuated at short ventricular cycle lengths (300 ms). In addition, ventricular refactoriness followed a similar curve to that of the ventricular APD. Similar results in animals have been reported with the new class III agent dofetilide (UK68798).$^{50}$

Effects on Ventricular Arrhythmias

Our data indicate that isolated or selective prolongation of ventricular APD and refactoriness was the crucial determinant of efficacy of sematilide in preventing the induction of sustained ventricular tachycardia. While the ability to suppress inducible ventricular tachycardia during premature ventricular stimulation and to prevent ischemia-induced ventricular arrhythmias has been demonstrated in animal models with sematilide$^{25,28}$ and agents with similar electrophysiologic effects,$^{40,50}$ this is the first report describing ventricular antiarrhythmic effects of a “pure” class III agent in humans. In our study, 28% of the patients had their inducible sustained ventricular tachycardia completely suppressed and an additional 16% had a partial response (ie, inducible nonsustained ventricular tachycardia of more than 15 beats). In patients who continued to have inducible sustained ventricular tachycardia while on sematilide, the ventricular tachycardia cycle length was modestly, but significantly, increased.

We found no effects of sematilide on conduction velocity; thus, it is probable that suppression of inducible ventricular tachycardia and the increase in observed ventricular tachycardia cycle length were secondary to increases in ventricular refactoriness. However, it is possible that an agent that solely prolongs refractoriness may still slow conduction within a reentrant circuit if the leading edge of the circulating impulse encroaches on tissue from the previous cycle that is still within the relative refractory period. The finding that the tachycardia cycle length increased secondary to increases in refactoriness is consistent with the recent observation that amiodarone-induced prolongation of the ventricular tachycardia cycle length was directly (and significantly) related to ventricular effective refractory period prolongation by amiodarone but not to changes in conduction velocity (ie, sodium channel activity).$^{51}$

The reverse frequency-dependence of selective type III agents has resulted in some investigators questioning their usefulness for the treatment of patients with ventricular arrhythmias. For example, Hondeghem and Snyder$^{38}$ have raised the issue that because class III agents have a diminution of their electrophysiologic effects (ie, APD prolongation) at the short cycle lengths frequently observed in ventricular tachyarrhythmias, they may not have a high level of clinical efficacy. However, by decreasing the diastolic window, these agents may inhibit a premature ventricular complex from triggering reentry. In addition, pure class III agents may create bidirectional block by rendering a critical limb of the reentrant circuit refractory and thus decreasing the possibility that reentry would start or become sustained. Such a hypothesis is supported by our finding that prolongation of refactoriness by sematilide was the only examined clinical or electrophysiologic variable associated with the suppression of inducible sustained ventricular tachycardia. Nevertheless, although our data indicate that sematilide demonstrated reverse frequency dependence, it may still exert discernible effects during short cycle lengths. For example, even at the short ventricular pacing cycle length of 300 ms, there was a trend for sematilide to prolong the APD compared with baseline (6.2% increase; $P=.06$) and the ventricular effective refractory period was significantly increased (6.6%, $P=.008$). In addition, it is also possible that the specific electrophysiologic effects of the drug on the diseased tissue of the reentrant circuit may be somewhat different than those measured in more normal myocardial tissue. Whether different potassium blockers might exert different electrophysiologic actions on diseased tissues is unknown. Sematilide exerted only a modest effect on premature ventricular complex suppression, which was not related to suppression of inducible ventricular tachycardia. Thus, it is unlikely that premature ventricular complex suppression would play an important role in the antiarrhythmic effects of this agent.

Sematilide prevented inducible sustained ventricular tachycardia and/or ventricular fibrillation (complete responders) in 26% of patients exposed to sematilide (28% of patients undergoing electrophysiologic study on sematilide), and this is comparable to that reported in a recent review of the literature for quinidine (mean±SD, 22±9%) as well as for procainamide (23±9%).$^3$ Both of these latter agents delay conduction as well as prolong the ventricular APD. In addition, both compounds exhibit reverse frequency-dependency with respect to repolarization.$^{38,39,52}$ Recently, several reports$^{8-9}$ have demonstrated that the efficacy of class Ia agents to suppress inducible sustained ventricular arrhythmias was correlated with prolongation of refactoriness and not slowing of conduction. Thus, it is possible that
quinidine and procainamide mediate their beneficial effects on inducibility by a similar mechanism as sematilide. Whether such an effect might be correlated with their specific actions on myocardial potassium channels and their kinetics remains speculative.

Antiarrhythmic, Proarrhythmic, and Other Adverse Effects of Sematilide

The small numbers of patients discharged on sematilide therapy do not permit drawing definitive conclusions regarding the drug’s long-term antiarrhythmic efficacy. This will require a larger study. However, two of the discharged patients (25%) developed sudden cardiac death, and another had recurrent sustained ventricular tachycardia (12.5%). The reasons for the seemingly high arrhythmia recurrence are not clear. However, one patient with acute congestive heart failure may have manifested proarrhythmia; he had frequent runs of nonsustained ventricular tachycardia recorded 2 days before his death. Whether a run of rapid ventricular tachycardia may have resulted in significant attenuation of sematilide-induced prolongation of refractoriness (secondary to the reverse frequency-dependent effects of sematilide on repolarization), with a resulting sustained ventricular arrhythmia, is speculative. It is also possible that autonomic factors may have played a role in these patients’ arrhythmia recurrence. Recent studies have shown significant attenuation of quinidine-53-55 or amiodarone-56,57 induced prolongation of refractoriness during either isoproterenol or epinephrine administration. A preliminary study has also shown marked reduction of sematilide-induced prolongation of the ventricular effective refractory period and APD90 during isoproterenol administration.58 Indeed, two of the three arrhythmic events occurred while the patients were presumably in a high catecholaminergic state (vigorous exercise or marked congestive heart failure). Thus, it is possible that increased sympathetic tone resulted in an attenuation of sematilide-induced prolongation of repolarization and arrhythmia recurrence.

Although sematilide was generally well tolerated during the in-hospital phase of this study, one patient manifested pause-dependent runs of nonsustained ventricular tachycardia in the setting of QT prolongation. Such an effect is consistent with the electrophysiologic actions of the drug, because all class III agents may cause torsade de pointes, presumably by provoking early afterdepolarizations due to triggered activity.59-61 Afterdepolarizations have been demonstrated after sematilide administration in both canine cardiac Purkinje fibers58 and rabbit ventricular myocardium.57 Sotalol causes torsade de pointes in approximately 5% of patients,62 whereas the incidence with amiodarone has been low.63 The precise mechanisms for these differences is not understood. As illustrated by our patient, pause-dependent nonsustained ventricular tachycardia and torsade de pointes represent an inevitable adverse reaction in a proportion of patients given class III agents and may develop in patients who respond acutely to the drug.

Two patients developed gastrointestinal or neurological symptoms on higher doses of sematilide after having tolerated lower doses. Two of the three patients in whom sematilide was tried at 200 mg every 8 hours had to have the therapy discontinued secondary to symptoms or excessive QT prolongation. Despite the fact that 11 patients had a left ventricular ejection fraction of 0.30 or less, no patient developed worsening congestive heart failure or new congestive heart failure after having been started on sematilide. In this respect, it is pertinent to note that the increase in APD in animal studies using the class III agents sotalol and amiodarone was associated with an increase in contractile force.60,64,65

Study Limitations

This investigation had the following limitations. (1) It was not possible to assess the effects of ventricular paced cycle lengths of less than 300 ms because of hemodynamic instability or of more than 600 ms because of atrial interference. (2) QRS duration was used as a measure of overall ventricular conduction velocity, but this may not be as accurate as directly measuring conduction velocity. However, determination of the frequency-dependent conduction slowing using the QRS duration has been shown to highly correlate in vivo with Vmax blockade in vitro.60 (3) Plasma sematilide levels were not available. (4) It was not possible to accurately assess the long-term clinical efficacy of sematilide because the patient cohort was too small. This will require a larger study. (5) We measured the right ventricular apex effective refractory period and APD90, and the results may not fully reflect the electrophysiologic effects of sematilide on the patient’s arrhythmia circuit. It is possible that such diseased and, possibly, partially depolarized tissue might respond in a somewhat different manner to potassium channel blockade with sematilide.

Conclusions

This study demonstrates that isolated selective action potential prolongation is an effective mechanism to prevent the induction of sustained ventricular arrhythmias during electrophysiologic testing in humans. Sematilide HCl is a selective class III agent that manifests reverse frequency-dependent effects on the APD and ventricular refractoriness, does not appear to have sodium channel–blocking activity, and was symptomatically well tolerated. The 4% incidence of new pause-dependent nonsustained ventricular tachycardia and the occurrence of one possible proarrhythmic related death are of concern. Larger studies are warranted to determine sematilide’s long-term clinical efficacy and incidence of proarrhythmia in the treatment of patients with ventricular arrhythmias.

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