Effects of Flecainide in Patients With New SCN5A Mutation Mutation-Specific Therapy for Long-QT Syndrome?

J. Benhorin, MD; R. Taub, RN; M. Goldmit, MSc; B. Kerem, PhD; R.S. Kass, PhD; I. Windman, PhD; A. Medina, MD

Background—Mutations in the cardiac sodium channel gene (SCN5A) can cause one variant of the congenital long-QT syndrome. The effects of some of these mutations on the α-subunit channel properties can be blocked by type Ib antiarhythmic drugs. Recently, we have described a new SCN5A mutation (D1790G) that affects the channel properties in a manner suggesting that sodium blockers of the Ib type will be ineffective in carriers of this mutation. Hence, the ECG effects of flecainide-acetate, a type Ic sodium blocker, were evaluated in carriers of this mutation.

Methods and Results—Eight asymptomatic mutation carriers and 5 control subjects were studied. Intravenous lidocaine was tested first in only 2 mutation carriers and had no significant effect on any ECG parameter. Flecainide significantly shortened all heart rate–corrected repolarization duration parameters only in carriers and not in control subjects: QTc shortened by 9.5% (from 517±45 to 468±36 ms, P=0.011), and the S-offset to T-onset interval shortened by 64.7% (from 187±88 to 66±50 ms, P=0.0092). Flecainide also normalized the marked baseline repolarization dispersion in most mutation carriers. These effects among carriers were maintained during long-term (9 to 17 months) outpatient flecainide therapy with no adverse effects.

Conclusions—This report is the first to describe SCN5A mutation carriers who significantly responded to flecainide therapy yet did not respond to lidocaine. These results have important implications for long-QT allele–specific therapeutic strategies. (Circulation. 2000;101:1698-1706.)

Key Words: long-QT syndrome • genetics • sodium (ion) channels

The long-QT (LQT) syndrome is an inherited cardiac disorder associated with prolonged ventricular repolarization and a propensity for recurrent syncpe and sudden cardiac death caused by malignant ventricular arrhythmias.1,2 Initial linkage studies have demonstrated genetic heterogeneity in this disorder3,4 whereas currently, LQT has been linked to at least 5 chromosomal loci: 11p15.5 (LQT-1), 7q35-36 (LQT-2), 3p21-24 (LQT-3), 4q25-27 (LQT-4), and 21q22.1-22.2 (LQT-5), with several mutations reported for all loci except LQT-4.5–13 The SCN5A gene, which in its mutant forms causes LQT-3, encodes the α-subunit of the human cardiac sodium channel.14–16 Three SCN5A mutations have been reported to cause LQT syndrome in several North American and European families8,9: a 9 base-pair deletion (Δ-KPQ) and 2 missense mutations (R1644H and N1325S). An additional sporadic SCN5A mutation (R1623Q) has been identified in Japan.17

These mutations of the SCN5A gene prolong repolarization by promoting sodium entry into myocardial cells during the plateau phase of the action potential.18,19 Hence, it has been hypothesized that sodium cannel blockers might shorten ventricular repolarization in LQT-3. Such an effect was demonstrated by Schwartz et al,20 who reported shortening of the QT interval in 7 Δ-KPQ mutation carriers by administration of oral mexiletine. Rosero et al21 reported QT interval shortening in 2 carriers of the Δ-KPQ mutation by short-term administration of intravenous lidocaine and long-term tocainide therapy. A functional study of the Δ-KPQ mutation subsequently demonstrated that lidocaine can inhibit the plateau-phase sodium current leak.22 Recently, we have described a large LQT-3–affected kindred with a new SCN5A mutation: D1790G.23 Further functional cellular studies of the D1790G mutation have suggested that type Ib sodium blockers might be ineffective in carriers of this mutation.24 Thus, the purpose of this study was to evaluate the effects of short-term and long-term oral flecainide-acetate therapy (type Ic sodium blocker) in carriers of this mutation.

Methods

Patient Population

The study population consisted of 8 medication-free asymptomatic carriers of the D1790G SCN5A mutation (4 female subjects) and 5 control subjects (3 female subjects). All carriers were members of a single, large, Jewish, LQT-3–affected family that has been previ-
Figure 1. Partial LQT pedigree. Affected individuals (D1790G mutation carriers) are represented by circles (females) or squares (males) with solid left upper quadrants, unaffected individuals by empty left upper quadrant symbols, and those with unknown genotype by no left upper quadrant symbol; consanguineous marriages are represented by 2 horizontal lines and vertical arrows; deceased individuals by diagonal line from top right to bottom left; LQT-related death by single asterisk; LQT-related symptoms among living individuals by 2 asterisks; and dextrocardia by right-sided heart symbol; 8 mutation carriers who participated in this study are represented by sequential arabic numbers. Pedigree structure has been altered to protect confidentiality.

Study Protocol

All drug trials among mutation carriers were performed in-hospital over a period of 8 days. Intravenous lidocaine was tested first in only 2 mutation carriers; oral flecainide-acetate was tested then in all 8 carriers and the 5 control subjects. Lidocaine was given as an intravenous bolus at a dose of 1 mg/kg, followed by an infusion at a rate of 3 mg/min for 2 hours. Twelve-lead ECG recordings were recorded every 15 minutes for 6 hours, starting 2 hours before and ending 2 hours after lidocaine administration. Twenty-four hours after lidocaine administration, all carriers were first studied in a drug-free state for 24 hours by multiple 12-lead ECG recordings and a 24-hour Holter recording (Burwick Inc, digital recorder).

ECG Parameters

ECG parameters were manually measured on 4 to 5 ECG recordings per patient for each off-drug period (second 24 hours for carriers, 1 to 5 weeks before flecainide therapy for control subjects) and on-drug period (sixth day on therapy for carriers, 1 to 5 weeks on therapy for control subjects). Averages of off-drug and on-drug values were then compared by use of a 2-sided, paired t test. ECG parameters included the following intervals: R-R, PR, QRS, QT, QTc, SoTon, and SoTof. All were measured in limb lead II (lead III in patients with dextrocardia) on 3 consecutive beats and averaged. Repolarization parameters (QT, QTc, SoTon, SoTof) were corrected for heart rate by the use of Bazett’s formula. Holter recordings were analyzed for ventricular ectopic activity and for mean heart rate, standard deviation, and its 24-hour distribution.

Results

Baseline Clinical Characteristics

Familial relations among the studied carriers and other features of their families are described in Figure 1. All control subjects had normal left ventricular function and a history of paroxysmal atrial fibrillation: 2 had mild hypertension, 2 had mitral valve disease, and 1 had ischemic heart disease. Carriers were significantly younger than control subjects (32±12 vs 64±11 years, respectively, P=0.0013).

Lidocaine Effects

Lidocaine effects were first tested in only 2 carriers (Table 1). There was no significant effect of lidocaine on any of the measured ECG parameters, including all those related to...
TABLE 1. Lidocaine Effects Among Mutation Carriers

<table>
<thead>
<tr>
<th>Patient</th>
<th>R-R, ms</th>
<th>QRS, ms</th>
<th>PR, ms</th>
<th>QT, ms</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Off</td>
<td>On</td>
<td>Off</td>
<td>On</td>
</tr>
<tr>
<td>6</td>
<td>835±107</td>
<td>887±49</td>
<td>95±6</td>
<td>103±6</td>
</tr>
<tr>
<td>7</td>
<td>880±14</td>
<td>903±56</td>
<td>83±5</td>
<td>83±5</td>
</tr>
</tbody>
</table>

All values are mean±SD. “Off” denotes off lidocaine (drug-free baseline); “on” denotes on lidocaine.

TABLE 1. Continued

<table>
<thead>
<tr>
<th>QTc, ms</th>
<th>QTa–c, ms</th>
<th>SoTonc, ms</th>
<th>SoTofc, ms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Off</td>
<td>On</td>
<td>Off</td>
<td>On</td>
</tr>
<tr>
<td>491±5</td>
<td>492±9</td>
<td>398±12</td>
<td>400±23</td>
</tr>
<tr>
<td>506±13</td>
<td>490±20</td>
<td>429±6</td>
<td>416±19</td>
</tr>
<tr>
<td>418±18</td>
<td>403±14</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

repolarization duration (QT, Q onset to T-wave offset; QTc, Q onset to T-wave apex; SoTon, S offset to T-wave onset; SoTof, S offset to T-wave offset; subscript c as in SoTon, and SoTof, denotes heart rate correction according to Bazett).

Baseline ECG Characteristics
Most baseline ECG characteristics differed between carriers and control subjects (Table 2). QRS duration and the PR interval were significantly more prolonged among carriers than among control subjects. QTc and all other repolarization duration parameters were significantly more prolonged (P<0.01) as well among carriers than among control subjects, except for SoTonc (borderline statistical significance).

Flecainide Effects
The average daily flecainide dose was higher in control subjects than in carriers (260±55 vs 188±23 mg, respectively), as were their corresponding flecainide plasma levels (806±110 vs 491±164 ng/mL, respectively, P=0.002).

A representative example of a 12-lead ECG pair (baseline vs flecainide) in mutation carrier No. 5 is presented in Figure 2. As can be noted, flecainide induced some increase in heart rate, a marked shortening of repolarization duration, a normalization of most baseline T-wave abnormalities, and a prominent decline in T-wave amplitude in most leads. Figure 3 depicts an example of the marked repolarization heterogeneity at baseline and its normalization with flecainide: The marked dispersion of repolarization duration as well as that of T-wave morphology and amplitude at baseline all normalized with flecainide, along with some increase in heart rate. Individual responses among all carriers and control subjects are depicted in Figure 4.

A summary of flecainide effects on ECG parameters of interest among control subjects and carriers (pooled results) is provided in Table 3 and Table 4, respectively. Flecainide significantly prolonged the QRS, PR, QT, QTc, and QTa–c intervals, whereas it had no significant effects on R-R and all other heart rate–corrected repolarization parameters among control subjects (Table 3). However, among carriers, flecainide caused a decrease in R-R interval (P=0.015), a significant PR and QRS interval prolongation, and a significant shortening (P<0.03) of all repolarization duration parameters (Table 4): QTc decreased from 517±45 to 468±36 ms, respectively (a 49-ms [9.5%] decrease), and the QTa–c, decreased by 49 ms (10.8%). SoTonc and SoTofc, both of which do not contain the QRS interval, decreased by 64.7% and 16.5%, respectively. A graphic presentation of flecainide effects on heart rate–corrected repolarization parameters among carriers and control subjects is depicted in Figure 5.

Flecainide effects on all measured ECG parameters did not significantly change during long-term (9 to 17 months) follow-up in carriers and control subjects. Twenty-four–hour Holter monitoring before and after flecainide administration was performed only among carriers. Preflecainide and postflecainide recordings did not reveal any ventricular ectopic activity in all carriers. Holter recordings were suitable for heart rate analysis in only 5 of 8 carriers (Table 5).

Flecainide induced a significant decrease in mean R-R interval only in 3 carriers. Figure 6 depicts the R-R interval histograms (baseline vs flecainide) in mutation carrier No. 7. As can be noted, flecainide induced a marked shift to the left of the R-R histogram that corresponds to increased heart rate, mainly by eliminating its right-sided tail.

Discussion
The main findings of this study indicate that short-term and long-term flecainide therapy induced significant shortening of repolarization among LQT-3-affected patients who are carriers of the D1790G mutation. It is also the first report of
Figure 2. Standard 12-lead ECGs of mutation carrier No. 5 before (baseline, top) and after (bottom) flecainide therapy.
SCN5A mutation carriers who did not exhibit repolarization shortening with intravenous lidocaine.

**Functional Cellular Studies of SCN5A Mutations**

Previously studied SCN5A LQT-3 mutations have been shown to encode voltage-gated $\alpha$-subunit sodium channels that fail to completely inactivate during prolonged depolarizations.[17–19,22,25] Hence, it was predicted and then verified in clinical[20,21] as well as cellular[17–19,22,26,27] studies that type Ib sodium blockers such as lidocaine can normalize the defective channel properties caused by these previously reported mutations. However, the functional consequences of the $D1790G$ LQT-3 mutation were somewhat different. There was little effect on the biophysical properties of monomeric $\alpha$-subunits of the sodium channel, whereas a significant effect was observed in heteromeric channels formed by coexpression of $\alpha$-subunits and $\beta_1$-subunits: It did not promote a detectable sustained inward sodium current but rather caused a negative shift in steady-state inactivation.[24] Therefore, it was predicted that carriers of the $D1790G$ mutation will not respond to lidocaine, as do carriers of other SCN5A mutations. The lack of response to lidocaine in 2 carriers in the present study was therefore not surprising. However, in view of the fact that the findings of the functional cellular study of the $D1790G$ mutation[24] do not fully explain the phenotype (prolonged QT) in carriers of this mutation, further characterization of this mutation in cellular models, preferably with flecainide, are needed.

**Specific ECG Effects of Flecainide Among Mutation Carriers**

At baseline, carriers had, as expected, significantly more prolonged heart rate–corrected repolarization duration parameters than did control subjects. However, they also had significantly more prolonged PR and QRS intervals, though still within normal limits. Thus, despite the fact that the functional cellular study of the $D1790G$ mutation was conducted with holding potentials of near $-90$ mV,[24] this mutation probably does have some effect on channel availability in ventricular cells (that have similar resting potentials). Flecainide-induced shortening of repolarization duration parameters among carriers was most pronounced in terms of the SoTon interval (64.7% reduction, $P=0.0092$).

The fact that QTc significantly shortened among carriers but “only” by 9.5%, whereas it became more prolonged among control subjects, is related to the flecainide-induced QRS prolongation that was observed among both carriers and control subjects. In fact, the heart rate–corrected S offset to T offset (SoToTofc) interval, which excludes the QRS, did shorten with flecainide by 16.5% ($P=0.045$) only among carriers. Corrective effects of flecainide on repolarization appeared to be more prominent among carriers with more pronounced QTc prolongation at baseline (Figure 4). This trend might be related to the effects of modifier genes (undefined yet) or to possible flecainide effects on ionic channels other than SCN5A. Flecainide-induced normalization effects on the marked dispersion of repolarization among carriers in this study were most pronounced (Figure 3). These effects were not systematically quantified because of the complexity of the

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**Figure 3.** Superimposed Q-wave onset–synchronized V1 through V6 precordial leads before (baseline, top) and after (bottom) flecainide therapy in mutation carrier No. 5. Both tracings were generated with identical amplitude and time scales.
baseline repolarization dispersion observed: dispersion of duration, amplitude, and morphology, all of which tended to normalize with flecainide. The mild effect of flecainide on heart rate in some carriers provides, for the first time, some evidence that could indirectly explain the propensity of sinus bradycardia in some variants of LQT syndrome, especially LQT-3. This might be related to the fact that mutated sodium channels could be functionally active in the sinus node or nearby cells. Because sinus node cells are chronically depolarized in comparison to ventricular cells that are fully polarized, sinus node cells may be more susceptible to a mutation-induced decrease in sodium channel availability. This may cause slowing of heart rate, which is a central phenotypic feature of several LQT variants. Interestingly,
several family members of the mutation carriers reported in this study do have a relatively slow heart rate, including 3 cases with documented sinus arrest.

**Possible Mechanisms of Flecainide Effects Among Mutation Carriers**

Flecainide, as other type Ic agents, dissociates (unblocks) relatively slowly after it binds primarily to activated sodium channels and is capable of producing strong use-dependent block of sodium channels. Several previous studies by Antzelevitch et al. have demonstrated that epicardial, endocardial, and M cells are electrophysiologically heterogeneous, whereas the effects of sodium channel blockade are heterogeneous across different myocardial layers. Flecainide has been shown to cause either prolongation or marked abbreviation of action potential duration in epicardial cells but only a slight prolongation or abbreviation in endocardial cells in a canine cellular model. This differential effect on action potential duration was more pronounced at faster stimulation rates. Therefore, one can hypothesize that the electrophysiological derangement in D1790G mutation carriers differentially affects different myocardial layers, depending on the functional distribution of α-subunits and β1-subunits of the mutated sodium channel in these layers. The differential effects of flecainide might be “reciprocal” to the effects of the D1790G mutation, thereby allowing the drug effects demonstrated among carriers in this study. In addition, because the transient outward current (Ito) has been shown to be expressed differentially across the myocardial wall and flecainide has been shown to block channels encoded by the Kv4.2 α-subunit, a major molecular determinant of Ito, it is possible that Ito block contributed to the therapeutic effects of flecainide demonstrated in this study. The exact mechanism by which flecainide exerts its functionally corrective effects on D1790G-mutated channels is not clear currently and probably will be better defined by further functional cellular studies with flecainide in mutant cells carrying the D1790G and other LQT-3–related SCN5A mutations.

**Study Limitations**

Flecainide effects were studied among a limited number of carriers and control subjects. However, the observed effects were significantly different between carriers and control subjects. All control subjects had paroxysmal atrial fibrillation; however, none had other concomitant disorders such as the sick sinus syndrome that might be familial. Control subjects were significantly older than mutation carriers, yet this imbalance is overweighed by the fact that none had baseline conduction abnormalities that might be age related.

**Clinical Implications**

The results of the present study indicate that flecainide significantly shortened repolarization among D1790G muta-
tion carriers and not among control subjects. Flecainide also had corrective effects on repolarization dispersion and some mild effects on heart rate, all of which were maintained during long-term therapy without adverse effects. These salutary effects are encouraging, yet whether they can be associated with symptomatic and prognostic improvement among carriers must await further larger-scale controlled clinical trials. The fact that this is the first report to describe SCN5A mutation carriers who did not respond to intravenous lidocaine yet significantly responded to oral flecainide therapy indicates a possible by-mutation heterogeneity that might exist in LQT-3. However, just recently, after the completion of this study, flecainide effects similar to those we describe here have been observed in 4 LQT-3 patients who are carriers of the Δ-KPQ mutation (A.J. Moss, personal communication). Therefore, further studies that will assess the effects of flecainide in LQT-3–affected patients who are carriers of other SCN5A mutations are needed to finally determine whether the flecainide effects demonstrated in this study are mutation specific or gene specific. The results of such studies together with the results of this study will have important implications for strategies to treat LQT with a gene-specific approach. We do not recommend the use of flecainide in the Brugada syndrome, which has been associated with other SCN5A mutations that cause a loss of function as opposed to a gain of function caused by most LQT-3–related SCN5A mutations.

Acknowledgment

This study was supported in part by National Institutes of Health grant 5R01-HL-33843.

References

1706  Circulation  April 11, 2000


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_Circulation_. 2000;101:1698-1706
doi: 10.1161/01.CIR.101.14.1698

_Circulation_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

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