The Elusive Link Between LQT3 and Brugada Syndrome
The Role of Flecainide Challenge

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Background—Defects of the SCN5A gene encoding the cardiac sodium channel are associated with both the LQT3 subtype of long-QT syndrome and Brugada syndrome (BS). The typical manifestations of long-QT syndrome (QT interval prolongation) and BS (ST segment elevation in leads V1 through V3) may coexist in the same patients, which raises questions about the actual differences between LQT3 and BS. Intravenous flecainide is the standard provocative test used to unmask BS in individuals with concealed forms of the disease, and oral flecainide has been proposed as a treatment option for LQT3 patients because it may shorten their QT interval.

Methods and Results—We tested the possibility that in some LQT3 patients, flecainide might not only shorten the QT interval, but also produce an elevation of the ST segment. A total of 13 patients from 7 LQT3 families received intravenous flecainide using the protocol used for BS. As expected, QT, QTc, JT, and JTc interval shortening was observed in 12 of the 13 patients, and concomitant ST segment elevation in leads V1 through V3 (≥2 mm) was observed in 6 of the 13.

Conclusions—The data demonstrate that flecainide may induce ST segment elevation in LQT3 patients, raising concerns about the safety of flecainide therapy and demonstrating the existence of an intriguing overlap between LQT3 and BS. (Circulation. 2000;102:945-947.)

Key Words: long-QT syndrome • Brugada syndrome • arrhythmia • drugs

Methods

Clinical Evaluation
The 13 consecutively genotyped LQT3 patients included in the present study underwent a complete, noninvasive cardiac evaluation at our clinical center. Physical examination, ECG, exercise stress test, and 12-lead Holter recording were performed. Long-QT syndrome was diagnosed based on standard criteria.6

Flecainide was administered intravenously at a dose of 2 mg/kg over 10 minutes. A standard 12-lead ECG was continuously monitored during the test and for the following 30 minutes.

Molecular Screening
Genomic DNA was extracted from peripheral blood lymphocytes by standard techniques. The region of SCN5A encoding the cardiac sodium channel α-subunit was screened using single-strand conformation polymorphism on polymerase chain reaction–amplified genomic DNA samples. The abnormal conformers were directly sequenced using an ABI310 genetic analyzer or were cloned (TopoTA cloning, Invitrogen) and sequenced using plasmid-specific oligonucleotides. Shifts in single-strand conformation polymorphism were also checked against a panel of genomic DNA from 300 healthy reference individuals (600 chromosomes). In all patients, the presence of a second mutation in the remaining long-QT syndrome–related genes was excluded by molecular analysis.
Statistical Analysis

Data are expressed as mean ± SD. Statistical analysis was performed using the SPSS statistical package. A paired t test was used for the evaluation of changes in ECG parameters before and after flecainide; significance was accepted for P < 0.05. Linear regression analysis was used to assess the correlation between variables.

Results

The mean age of the 13 LQT3 patients (7 men) was 37 ± 18 years. Seven were symptomatic for repeated syncope, and 2 had been hospitalized for incessant runs of torsade de pointes. The QT interval was prolonged in 12 of the 13 patients (mean QT, 501 ± 45 ms; mean QTc, 504 ± 39 ms), and one had right bundle branch block. The patient with a normal QT interval was referred to our attention for the evaluation of presyncopal events. Mutations identified in SCN5A were ΔKPQ 1505 to 1507 (n=1), E1784K (n=3), V411M (n=1), ΔK1500 (n=5), R1626P (n=1), T1304M (n=1), and P2006A (n=1).

Flecainide administration significantly prolonged the PQ interval (from 164 ± 23 to 186 ± 22 ms; P < 0.001), widened the QRS interval (from 104 ± 25 to 126 ± 24 ms; P < 0.001), and shortened the QT (from 502 ± 45 to 460 ± 30 ms; P < 0.0001), QTc (from 504 ± 39 to 473 ± 28 ms; P < 0.01), JT (from 397 ± 54 to 334 ± 34 ms; P < 0.001) and JTc intervals (from 399 ± 51 to 347 ± 29 ms; P < 0.001; Figure 1). The RR interval was slightly but consistently reduced in all patients (from 981 to 931 ms; P < 0.05). The mean percent reduction of JTc (JTc\%\(\)) was 12.4% (range, 2% to 20%). The patient with no change in JTc\%\(\) was the patient with a normal QT interval at baseline. Only a modest correlation was present between JTc at baseline and the JTc\%\(\) reduction after flecainide (r² = 0.58). No correlation was observed between JTc\%\(\) and RR shortening (r² = 0.036) or between JTc\%\(\) and QRS widening (r² = 0.034).

ST segment elevation in leads V1 through V3 (≥ 2 mm) after flecainide occurred in 6 of the 13 patients; these 6 patients had trend toward a shorter baseline QTc and JTc compared with patients without ST segment elevation (JTc, 372 ± 26 versus 424 ± 56; P = 0.006). No difference in the shortening of QT, QTc, JT, JTc, or JTc\%\(\) after flecainide was observed between the patients with (n=6) and without (n=7) ST segment elevation. ST segment elevation occurred in a similar percentage of symptomatic and asymptomatic patients.
Two of the 7 mutations (ΔKPQ 1505 to 1507, E1784K) have been expressed in heterologous systems and are associated with the delayed fast inactivation of the sodium current. The development of ST segment elevation seemed unrelated to the specific mutations and to their electrophysiological effects. Not all patients with the same genetic defect had a concordant response to the flecainide test. Specifically, in a family with 3 carriers of the E1784K defect (baseline QTc of 496, 510, and 520 ms), QT shortening was observed in all patients, but only one developed marked ST segment elevation (Figure 2).

The patient with a normal QTc interval at baseline (Figure 1) is a carrier of the T1304M mutation that has been described in association with the LQT3 phenotype; he did not develop ST segment elevation after flecainide.

In one patient with a familial form of LQT3 in whom flecainide induced QT shortening and ST segment elevation, an analysis of ECGs recorded 30 years earlier revealed that twice he presented with spontaneous ST segment elevation.

Discussion

This study provides evidence that intravenous flecainide at the dose used to unmask concealed BS may induce ST segment elevation and QT shortening in LQT3 patients. The appearance of the ECG pattern that, according to current standards, is diagnostic for BS raises concerns about placing LQT3 patients on long-term treatment with flecainide. Ajmaline and flecainide administration was proposed by Brugada et al4 as a diagnostic test for the identification of concealed forms of BS. Accordingly, individuals with mild ST segment elevation and their family members are exposed to this provocative test and diagnosed as “affected” by BS whenever a 1-mm ST segment elevation occurs.4 We recently questioned the sensitivity of the flecainide test when we identified family members of BS probands who carried the genetic defect but failed to manifest ST segment elevation during pharmacological challenge (unpublished data). Data reported here show that flecainide administration may also induce ST segment elevation in leads V1 through V3 in LQT3 patients.

The rationale for using sodium channel blockers in LQT3 is based on the experimental evidence that mexiletine reduces the action potential prolongation produced by delayed inactivation of the sodium current and the persistent inward current associated with 3 mutations (ΔKPQ, R1644H, and N1325S).7 Indeed, acute oral testing with mexiletine shortened the QT interval in LQT3 patients.11

Recently, Benhorin et al3 reported that oral flecainide significantly shortened the QT interval in 8 asymptomatic members of one LQT3 family; intravenous administration of the drug was not done, and patients were placed on long-term treatment, with persistence of the QT interval shortening over time. Benhorin et al3 conclude by saying that the response to flecainide could be either gene-specific or mutation-specific. In fact, the picture could be even more complex: our data raise the possibility that it may be “individual specific.” In one family, all 3 affected members with marked QT interval prolongation had QT shortening with flecainide; however, the one with the more modest shortening (32 ms versus 58 and 64 ms) also developed ST segment elevation. Like the puzzling issue of incomplete penetrance, with some family members carrying the mutation but not manifesting QT prolongation, it may also be true that the response to sodium channel blockade shows individual variability or that it lacks reproducibility within the same patient. This raises uncertainties about the negative predictive value of the lack of ST segment elevation after the intravenous administration of flecainide and questions the overall safety of long-term treatment with flecainide in LQT3.

These findings prompt 2 considerations relevant to clinical practice. (1) The similar response of LQT3 and BS patients to flecainide challenge, combined with the common clinical features of the 2 diseases (suspected or certain lack of therapeutic efficacy of β-blockers, high lethality of cardiac events, and arrhythmias occurring at rest or sleep), demonstrates that the phenotypic overlapping of LQT3 and BS is larger than commonly appreciated. (2) The evidence that flecainide may provoke ST segment elevation calls for caution in initiating long-term flecainide treatment in LQT3 patients.

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References
