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Gene-Specific Therapy With Mexiletine Reduces Arrhythmic Events in Patients With Long QT Syndrome Type 3

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ABSTRACT

BACKGROUND Long QT syndrome type 3 (LQT3) is a lethal disease caused by gain-of-function mutations in the *SCN5A* gene, coding for the alpha-subunit of the sodium channel NaV1.5. Mexiletine is used to block late sodium current and to shorten QT interval in LQT3 patients.

OBJECTIVES The aim of this study was to determine whether mexiletine prevents arrhythmic events (arrhythmic syncope, aborted cardiac arrest, or sudden cardiac death) in LQT3 patients.

METHODS The endpoint of this retrospective cohort study, which studied consecutive LQT3 patients who were referred to our center and treated with mexiletine, was to evaluate the antiarrhythmic efficacy of mexiletine by comparing the number of arrhythmic events per patient and the annual rate of arrhythmic events during observation periods of equal duration before and after the beginning of therapy with mexiletine.

RESULTS The study population comprised 34 LQT3 patients, 19 (56%) of whom were male. The median age at beginning of treatment with mexiletine was 22 years, and median QTc interval before therapy 509 ms. The median duration of oral mexiletine therapy was 36 months, at an average daily dose of 8 ± 0.5 mg/kg. Mexiletine significantly shortened QTc (by 63 ± 6 ms; $p < 0.0001$) and reduced the percentage of patients with arrhythmic events (from 22% to 3%; $p = 0.031$), the mean number of arrhythmic events per patient (from 0.43 ± 0.17 to 0.03 ± 0.03; $p = 0.027$), and the annual rate of arrhythmic events (from 10.3% to 0.7%; $p = 0.0097$).

CONCLUSIONS Besides shortening QTc interval, mexiletine caused a major reduction of life-threatening arrhythmic events in LQT3 patients, thus representing an efficacious therapeutic strategy. (J Am Coll Cardiol 2016;67:1053–8)

Long QT syndrome type 3 (LQT3) is a rare variant of long QT syndrome (LQTS) caused by gain-of-function mutations in the gene *SCN5A*, coding for the sodium channel NaV1.5 (1). Based on reports that the incidence of LQTS in neonates is 1:2,000 (2) and that LQT3 accounts for approximately 10% of LQTS patients (3), the incidence of LQT3 is estimated at 1:20,000.

LQT3 is characterized by a severe prognosis (3,4) and an incomplete response to beta-blockers (5), as compared to LQTS type 1, the most common LQTS variant. Since arrhythmic events in LQT3 occur predominantly at rest (6), the value of beta-blocker therapy has been questioned (5,7), leaving the management of LQT3 patients uncertain.

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ABBREVIATIONS AND ACRONYMS

CI = confidence interval

ECG = electrocardiogram

LQT3 = long QT syndrome type 3

LQTS = long QT syndrome

This study is an extension of 2 pilot works we conducted in the late 1990s, when we demonstrated the ability of mexiletine to abbreviate the duration of ventricular repolarization in an animal model of LQT3 (8) and in LQT3 patients (9). Those preliminary observations led to an off-label use of mexiletine in LQT3 patients, targeted to shorten the QT interval; this off-label use is now recommended in clinical practice guidelines (10). Unfortunately, there is no evidence to support the hypothesis that, by shortening the QTc, this drug may also reduce the occurrence of life-threatening arrhythmias.

The objective of the study was to evaluate the ability of mexiletine to reduce the occurrence of arrhythmic events in LQT3 patients.

METHODS

We enrolled consecutive LQT3 patients referred to our center who accepted treatment with oral mexiletine. For each individual, we collected demographic data, personal and family history, symptoms, arrhythmic events, and therapy at follow-up, which was then stored in a customized database. Additionally, we stored electrocardiogram (ECG) parameters for rhythm, heart rate, and duration of PR, QRS, and QT intervals. In addition, we obtained 12-lead ECGs (paper speed 25 mm/s and 10 mm/mV sensitivity) at stable heart rates close to 60 beats/min during daylight hours to limit the confounding effect of diurnal variability of QT interval (11). The QT interval duration before and after therapy was measured in lead II, selecting beats preceded by similar RR intervals, as required when applying Bazett's formula.

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TERMS AND DEFINITIONS. Arrhythmic events included sudden cardiac death, aborted cardiac arrest (including appropriate implantable cardioverter-defibrillator [ICD] shocks), or syncope occurring in the absence of alternative explanations (e.g., orthostatic hypotension or vagally mediated episodes).

Symptomatic patients were defined as individuals who had experienced ≥1 arrhythmic event(s) before starting mexiletine.

We used several electrocardiographic terms. Baseline ECG was the ECG recorded at first visit, before starting mexiletine. ECG on therapy was used to describe the first ECG recorded after initiation of mexiletine, when the maximum-tolerated dose of mexiletine was administered. To verify whether the effect of mexiletine was maintained across the 24-h period, we added measurements of ECG parameters from the first Holter monitor recording obtained at our center on therapy, comparing QTc duration during "daytime" hours (at a heart rate of 60 beats/min) versus QTc duration at the slowest heart rate recorded during "night time."

STATISTICAL ANALYSIS. Statistical analysis was performed using SPSS software version 21 (IBM Corp., Armonk, New York). Continuous variables were expressed as median with interquartile range (IQR) or mean ± SE; comparisons were performed using paired and unpaired nonparametric tests as appropriate. Categorical variables were reported as absolute and relative frequencies and compared by Fisher exact or McNemar tests.

To evaluate the antiarrhythmic efficacy of mexiletine, a matched-period analysis was performed to compare arrhythmic events off and on mexiletine (12). For each patient, periods of equal duration before and after starting mexiletine were identified, with patients serving as their own controls. Two infants who initiated therapy in the first week of life were considered ineligible for the matched-period analysis because they had a pre-drug observation time of only 7 days; therefore, the analysis was conducted on 32 patients.

The number of arrhythmic events was determined for the matched periods and averaged over the number of patients. To assess the effect of mexiletine on event rates, a Poisson regression model was fitted using generalized estimating equations. Robust standard errors were computed to account for intrapatient correlation. The incidence rate ratio with 95% confidence interval (CI) was calculated to measure the impact of mexiletine on event counts over time. A value of $p < 0.05$ (2 sides) was considered statistically significant.

RESULTS

POPULATION CHARACTERISTICS. A total of 34 LQT3 patients (19 or 56% males) were enrolled. The mutations identified in the cohort are shown in **Figure 1**. Patients entered the study at the time of the first clinical visit to our center and the total observation time was 59 months (IQR: 29 to 144 months). Mexiletine was initiated at a median age of 22 years (IQR: 8 to 44 years); the median QTc at baseline ECG was 509 ms (IQR: 490 to 548 ms). Five infants younger than 1 year of age were referred to our center after experiencing a cardiac arrest (4 of 5) or a prolonged loss of consciousness (1 of 5); all of them had a QTc interval >550 ms.

Before starting mexiletine, 21 of 34 (62%) individuals were asymptomatic and 13 (38%) were