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ORIGINAL ARTICLE

Mexiletine Shortens the QT Interval in Patients With Potassium Channel–Mediated Type 2 Long QT Syndrome

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BACKGROUND: Long QT syndrome is a potentially lethal yet highly treatable cardiac channelopathy. Although β-blocker therapy is standard for most patients, concomitant therapy with sodium channel blockers, like mexiletine, is often utilized for patients with sodium channel–mediated type 3 long QT syndrome (LQT3). The potential role of sodium channel blockers in patients with potassium channel–mediated long QT syndrome (ie, LQT1 and LQT2) has not been investigated in detail.

METHODS: We performed a retrospective chart review on 12 patients (5 females; median age at diagnosis 14.1 years (interquartile range [IQR], 7.7–23; range, 0–59, median heart rate–corrected QT interval [QTc] at diagnosis 557 ms (IQR, 529–605) with genetically established LQT2 (10) or a combination of LQT1/LQT2 (1) or LQT2/LQT3 (1), who received mexiletine. Data were collected on symptomatic status, treatments, and breakthrough cardiac events after diagnosis and initiation of treatment. Additionally, 12-lead ECGs were collected at diagnosis, before initiation of mexiletine and following mexiletine to evaluate the drug's effect on QTc.

RESULTS: Before diagnosis, 6 patients were symptomatic and, before initiation of mexiletine, 4 patients experienced ≥1 breakthrough cardiac event on β-blocker. Median age at first mexiletine dose was 24.3 years (IQR, 14–32.4). After mexiletine, the median QTc decreased by 65±45 ms from 547 ms (IQR, 488–558) premexiletine to 470 ms (IQR, 409–529) postmexiletine (P=0.0005) for all patients. In 8 patients (67%), the QTc decreased by ≥ 40 ms with a mean decrease in QTc of 91 ms ($P < 0.008$). For the 11 patients maintained on mexiletine therapy, there have been no breakthrough cardiac events during follow-up.

CONCLUSIONS: Although commonly prescribed in patients with LQT3, mexiletine also shortens the QTc significantly in two-thirds of a small subset of patients with potassium channel–mediated LQT2. In patients with LQT2, pharmacological targeting of the physiological late sodium current may provide added therapeutic efficacy to β-blocker therapy.

VISUAL OVERVIEW: A visual overview is available for this article.

Key Words: long QT syndrome ■ mexiletine ■ potassium channels ■ sodium channel ■ sodium channel blockers

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WHAT IS KNOWN?

- Long QT syndrome is a genetic heart rhythm disorder characterized by prolongation of the ECG-derived QT interval leading to an increased risk of syncope, seizures or sudden cardiac death. Current treatment aimed at mitigating the risk of sudden cardiac death consists of β-blocker therapy, left-sided cardiac sympathetic denervation, and an implantable cardioverter defibrillator.
- Addition of the sodium channel blocker mexiletine in patients with sodium channel–mediated type 3 long QT syndrome (LQT3) has provided a significant reduction of arrhythmic events in patients with LQT3.

WHAT THE STUDY ADDS?

- We performed a retrospective analysis on the effect of mexiletine on patients with the second most common genetic subtype of LQTS, those with potassium channel–mediated, LQT2.
- Our data on a small group of selected, high-risk patients showed that mexiletine significantly reduced the QTc in short- and long-term follow-up. Additionally, no arrhythmic events occurred during follow-up.
- This study provides the first clinical evidence for the potential QT shortening effect of mexiletine in patients with LQT2 providing another possible treatment option for this subtype of long QT syndrome.

Long QT syndrome (LQTS) is a genetic heart rhythm disorder that affects ≈1 in 2000 individuals and is often characterized by prolongation of the ECG-derived, heart rate–corrected QT interval (QTc).[1] Although over 17 genes have been implicated in the pathogenesis of LQTS, the majority of mutations perturb the critical ion channel pore-forming α-subunits encoded by 3 genes: the *KCNQ1*-encoded Kv7.1 potassium channel (type 1 long QT syndrome [LQT1]), the *KCNH2*-encoded Kv11.1 potassium channel (LQT2), and the *SCN5A*-encoded Nav1.5 sodium channel (LQT3).[2,3] Clinically, although the majority of patients with LQTS may never experience a LQTS-triggered symptom, LQTS can cause syncope, seizures, or sudden cardiac death secondary to its hallmark arrhythmia of torsades de pointes and subsequenty ventricular fibrilation.[4,5]

Treatment of LQTS is, therefore, aimed at mitigating the risk for arrhythmias and sudden cardiac death and consists of pharmacological treatment (mainly β blocker (BB) therapy), left-sided cardiac sympathetic denervation,[6–8] or an implantable cardioverter defibrillator (ICD).[5,9] Although most patients are treated with a BB (preferably nadolol[4,10–12]), some genotype-specific pharmacological treatments have emerged. For example, although BB therapy is standard first-line therapy for the 3 major LQTS genotypes, BBs have genotype-dependent efficacy (LQT1>LQT2>LQT3) being most effective in preventing breakthrough cardiac events (BCEs) in patients with LQT1.[13–16] Similarly, left-sided cardiac sympathetic denervation's greatest efficacy is realized for patients with LQT1.[6,7,17] Conversely, sodium channel blocker therapy with medications like mexiletine are most effective as combination therapy with BBs in LQT3.[18–21]

At variance with the understandable rationale for assessing a sodium channel blocker in LQT3, caused by mutations which directly accentuate the late sodium current, a possible QT-shortening effect and therapeutic efficacy of mexiletine for patients with potassium channel–mediated LQTS has not received great attention. Here, we present a retrospective review and early assessment of the use of mexiletine and its effect on QTc and clinical outcomes in a small group of patients with LQT2.

METHODS

We performed a retrospective review of all patients with LQT2 who were evaluated and treated at either Mayo Clinic (Rochester, MN) or the IRCCS Istituto Auxologico Italiano (Milan, Italy) and who received mexiletine either via mexiletine challenge according to the acute oral drug testing methodology[22] or chronic administration. This study was approved by the Institutional Review Board under the guidelines of retrospective studies, and all data that support the findings of this study are available from the corresponding author on reasonable request. Mexiletine dose was targeted at 4 to 6 mg/kg per dose every 8 hours as per standard clinical practice. Clinical demographics, disease history, presentation and outcomes, family history, past and current treatments, and genetic data were extracted from the medical records. The effect of mexiletine was evaluated by analysis of the QTc before and after initiation of the drug, as well as at most recent follow-up on mexiletine. For the acute mexiletine studies performed in Italy, the first QTc postadministration was generally obtained after ≈2 hours to assess mexiletine's effect at its anticipated peak plasma levels consistent with its predicted pharmacokinetic properties. Additionally, a QTc from the patient's most recent follow-up while on mexiletine was obtained to determine the long term/chronic effect of the drug on their QTc. LQTS-related outcomes were evaluated for all patients. The QTc from the 12-lead ECG was evaluated and confirmed or corrected by an experienced genetic cardiologist (either Drs Crotti, Schwartz, or Ackerman), typically using the rhythm strip provided and limb lead II and precordial lead V5 for the QTc confirmation. The QTc used in this study was the QTc recorded at the time of the patient's clinical evaluation which preceded this retrospective study. A BCE was defined as an LQTS-attributable faint, seizure, cardiac arrest, or appropriate ventricular fibrilation–terminating ICD shock while on optimal treatment.

Statistical analyses were performed using JMP statistical software (JMP 13, SAS Institute Inc, Cary, NC), and continuous

Table 1. Patient Demographics

N	12
Male/female (n)	7/5
Median age at diagnosis, IQR, y	14.1 (7.7–23)
Symptoms before diagnosis, n (%)	4 (33)
Median QTc, IQR, ms	557 (529–605)
Diagnosis (n)	
LQT2	10
Combination	2 (LQT1/LQT2 and LQT2/LQT3)
Family history of LQTS, n (%)	6 (50)
Family history of SCD, n (%)	4 (33)
Therapy, n (%)	
β-Blocker	12 (100)
LCSD	4 (33)
ICD	1 (8)
Median age at mexiletine trial, IQR, y	32.4 (24.3–54.8)
Median QTc before mexiletine, IQR, ms	547 (488–558)
Median QTc following mexiletine, IQR, ms	470 (409–529)
Mean ΔQTc, ms	−65±45
Median QTc at follow-up, ms	464 (449–491)

ICD indicates implantable cardioverter defibrillator; IQR, interquartile range; LCSD, left-sided cardiac sympathetic denervation; LQT, long QT; LQTS, long QT syndrome; and QTc, heart rate–corrected QT interval.

variables were expressed as median and interquartile range (IQR). Comparisons were performed using nonparametric Wilcoxon rank-sum and matched-pair, Wilcoxon signed-rank test as appropriate. To evaluate the effect of mexiletine and determine the change in QTc (ΔQTc) before, immediately after, and at follow up for all patients matched-pair, Wilcoxon signed-rank tests were performed with each patient serving as his/her own control. For other comparisons, Wilcoxon rank-sum tests were used. A ΔQTc ≥40 ms was considered a clinically relevant response to mexiletine therapy.[23,24] A *P* value <0.05 was considered statistically significant.

RESULTS

Overall, 12 patients (5 females) with LQT2 were treated with mexiletine because of either extreme QT prolongation or for additional sudden cardiac death protection. Ten patients had a single, LQT2-associated variant in *KNCH2*, whereas there were 2 LQT2 patients who had an additional LQTS-associated variant in another gene, including 1 patient with a variant in *KCNQ1*-mediated LQT1 and 1 patient with a variant in *SCN5A*-mediated LQT3 (Table 1). The median age of diagnosis was 14.1 years (IQR 7.7–23.0 years) with a median QTc at first evaluation of 557 ms (IQR 529–605). Half of the patients (6/12, 50%) had experienced ≥1 LQTS-triggered cardiac event before their diagnosis of LQTS. At the time of their mexiletine trial, each patient was on BB therapy, 4 patients (33%) had undergone left-sided cardiac sympathetic denervation, and 1 patient (8%) had an ICD.

Of the 12 patients, 7 received mexiletine initially as an acute drug challenge while the remaining patients were treated with mexiletine intentionally as part of their LQT2-directed treatment program. Median age at start of mexiletine was 24.3 years (IQR, 13.4–32.3; range 2 days to 58 years old; Table 2). Mexiletine therapy was associated with an overall dramatic decrease of the median QTc from 547 ms (IQR, 488–558) ms before its initiation to 470 ms (IQR, 409–529) with a ΔQTc of −65 ms (*P*=0.0005; Figure 1). For 4 patients (30%; case 1, 3, 6, and 8), the QTc decreased below the proarrhythmic threshold of 500 ms during mexiletine therapy (Figure 2).

More importantly, in 8 of 12 patients (67%; 6 males, median age at diagnosis 21.3 years; IQR, 13–34), mexiletine resulted in a ≥40 ms decrease in QTc, classifying these patients as mexiletine responders (cases 1, 3, 4, 6, 8, 10–12), resulting in a significant decrease of median QTc from 547 ms (IQR, 476–593) to 436 ms (IQR, 395–511) with a mean ΔQTc of −91 ms (*P*=0.008; Figure 1). ECG examples of mexiletine responses are shown in Figure 3, as well as in the in the Data Supplement. The first patient (case 1) was a male patient diagnosed with LQT2 at age 12 without prior cardiac events but an extremely high QTc of 558ms at diagnosis, who showed a decrease of his QTc of 63 ms following mexiletine.The second patient (case 6) was a female patient, who had a prior cardiac arrest during an instance of high stress at work, whose QTc significantly decreased from 549 ms before mexiletine administration to 415 ms within 80 minutes of giving the drug, a decrease of 134 ms. Additional examples can be found in the in the Data Supplement. Among the 8 LQT2 mexiletine responders, 2 patients (case 4 and 12) had a second LQTS-associated mutation (LQT1 in case 4, LQT3 in case 12).

Overall, there were no significant differences between the phenotype of the ΔQTc ≥40 ms responders compared with the 4 patients classified as therapeutic nonresponders (ie, ΔQTc < 40 ms) with respect to sex (63% versus 50% male; *P*=1.0), median age at diagnosis (13 years; IQR, 7.2–21.3) versus 19 years (IQR, 8.6–49.7; *P*=0.4), symptoms before diagnosis (25% versus 50%; *P*=0.5), median age at start of mexiletine (24.3 years; IQR, 17.8–32.3 versus 20.8 years; IQR, 20.8; IQR, 11.1–50.3; *P*=0.8), median QTc at baseline (557 ms; IQR, 529–609 versus 564 ms; IQR, 502–596; *P*=0.7), and median QTc before mexiletine (547 ms; IQR, 476–593 versus 550 ms; IQR, 494–557; *P*=0.9), respectively. Similarly, there was no difference in the location of their LQT2-associated pathogenic variant (N terminus, linker-pore, or C terminus; 25% to 50% to 25% versus 37.5% to 25% to 37.5%; *P*=0.7 or type of variant (missense versus frameshift/terminating variant; 50% versus 50%; *P*=1.0), respectively. However, the

Table 2. Clinical Details of Patients Receiving Mexiletine

Case	Sex	Age at Mexiletine, y	Diagnosis	Variant(s)	Family History of LQTS and SCD	Symptomatic Before Diagnosis	LCSD and ICD	QTc at Diagnosis, ms	QTc Before Mexiletine Trial	QTc After Mexiletine, ms	ΔQTc	QTc at Follow-Up, ms	ΔQTc, ms	Follow-Up Time, y
1	Male	18.3	LQT2	KCNH2 F29V	None	No	LCSD	558	519	456	−63	452	−67	1.5
2*	Female	16.1	LQT2	KCNH2 N45D	None	Yes	LCSD/ ICD	545	544	528	−16	513	−31	0.4
3	Male	26.6	LQT2	KCNH2 A78P	LQTS	No	…	525	545	407	−138	420	−125	0.5
4	Female	2 days	LQT1/2	KCNQ1 R555H; KCNH2 P151fs179	LQTS	No	…	667	622	525	−97	491	−131	1.1
5*	Female	58.2	LQT2	KCNH2 W585X	LQTS/SCD	No	…	600	477	469	−8	469	−8	1
6	Female	34.3	LQT2	KCNH2 L589P	None	Yes	…	610	549	415	−134	466	−83	1.6
7*	Male	9.8	LQT2	KCNH2 G604S	None	Yes	…	582	556	547	−9	517	−39	3.7
8	Female	13.6	LQT2	KCNH2 N629S	SCD	No	…	540	558	470	−88	450	−108	0.3
9*	Male	26.6	LQT2	KCNH2 D803fs	None	No	…	487	557	531	−26	535	−22	0.1
10	Male	46.7	LQT2	KCNH2 P926Rfs48	LQTS	No	LCSD	480	462	387	−75	384	−78	1
11	Male	24.6	LQT2	KCNH2 P926Rfs48	LQTS/SCD	Yes	LCSD	606	604	529	−75	464	−140	1.1
12	Male	23.9	LQT2/3	KCNH2 W1001X SCN5A R814Q	LQTS/SCD	No	…	555	446	391	−55	449	3	0.9

ICD indicates implantable cardioverter defibrillator; LQT, long QT; LQTS, long QT syndrome; QTc, heart rate–corrected QT interval; and SCD, sudden cardiac death.
*Patients considered nonresponders to mexiletine therapy since the QTc shortening was <40 ms.

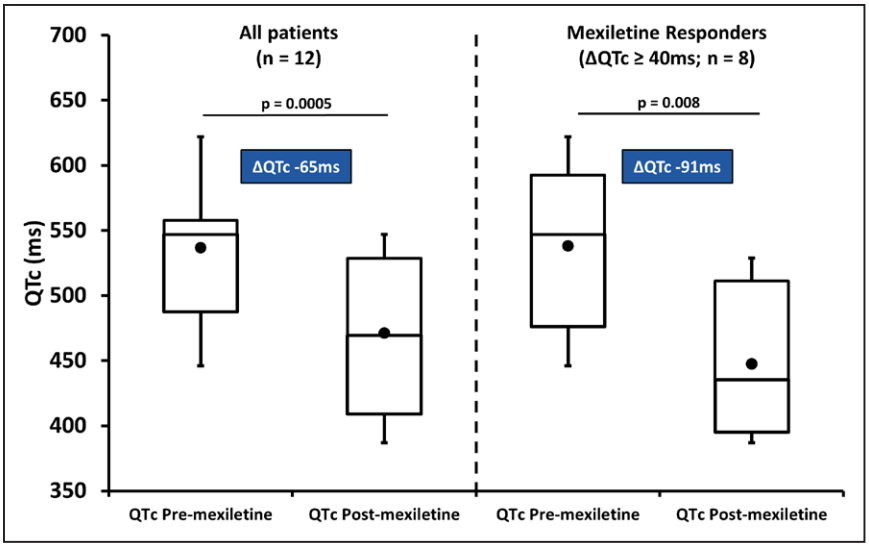

Figure 1. Heart rate–corrected QT interval (QTc) following mexiletine.
Box plot showing the median QTc (interquartile range) immediately before (**left**) and after mexiletine administration (**middle**). Matched-pair, Wilcoxon signed-rank test showed a significant decrease of mean QTc of −65 ms after 1.5 to 2 h of mexiletine (*P*=0.0005; **left**). Importantly, among patients showing shortening of the QTc of ≥40 ms, the median QTc decreased even more significantly by 91 ms (*P*=0.008; **right**).

small cohort size may prevent the identification of any potential differences that may help predict response to mexiletine.

Overall, 11 out of 12 patients remained on chronic mexiletine therapy, and for these patients, the reduction of QTc persisted with a median QTc of 464 ms (IQR, 449–491), still significantly reduced compared with their premexiletine QTc (*P*=0.002; ΔQTc, −73 ms), and unchanged when compared with their initial postmexiletine QTc (*P*=0.5; ΔQTc=−4 ms).

Mexiletine was fairly well tolerated, and although some patients reported gastrointestinal discomfort, this never led to discontinuation of the drug. In all, 4 of 12 patients (33%) complained of mild gastrointestinal discomfort, but this generally resolved after being on the mexiletine for a while. For 1 patient (case 10), gastrointestinal discomfort led to decrease of the mexiletine dose, which resulted in better drug tolerance. More importantly, none of these 12 patients have experienced a BCE while on mexiletine. However, given the short follow-up time (1.3±0.9 years; range 2 months to 3.7 years), it is too premature to draw definitive conclusions in terms of the degree of arrhythmic risk reduction.

DISCUSSION

While BB therapy is the mainstay treatment for the majority of patients with LQTS, the search for additional therapies, especially those that can potentially shorten the QT interval, continues. In this case series, we demonstrate in a small group of patients with LQT2 that, contrary to currently held views, the sodium channel blocker mexiletine can produce a substantial, and clinically relevant, shortening of the QTc among patients with LQT2.

The first proposal to use mexiletine for patients with LQTS, and specifically for patients with *SCN5A*-mediated LQT3, was made in 1995 and represented the first suggestion of gene-specific therapy aimed at shortening the QT interval by blocking the inward late sodium current.[18] The changes observed among a small number of LQT2, and later, of LQT1 patients were <30 ms and did not seem to be clinically meaningful.[18] Following the 1995 report, the use of mexiletine for LQT3 entered clinical practice, and combination therapy with BB and mexiletine has been part of the treatment guidelines for LQT3 since 2013[9, 21]. The present data, showing that the QTc shortened significantly in more than two-thirds of patients with LQT2 following mexiletine, provides encouraging data to potentially consider a trial of this drug in symptomatic patients with LQT2 and marked QT prolongation at rest (ie, QTc >500 ms) before imme-

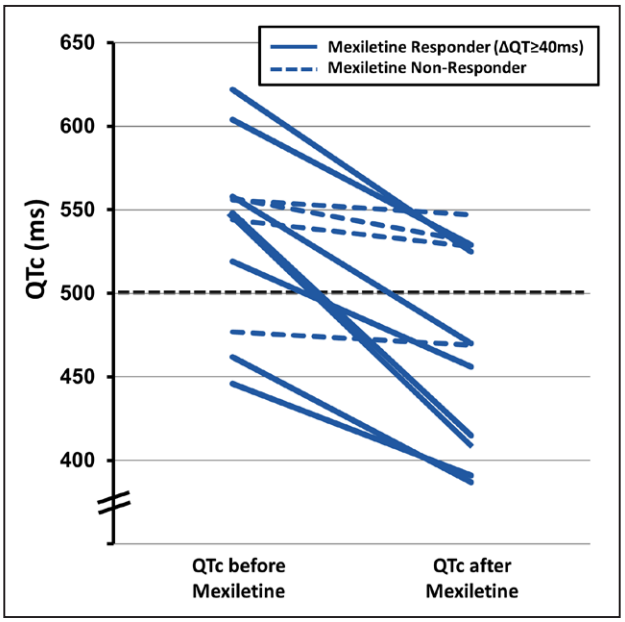

Figure 2. Effect of mexiletine on individual heart rate–corrected QT interval (QTc).
Line diagram showing effect of mexiletine for each individual patient. QTc decreased in all patients with 8 out of 12 (67%) showing a decrease ≥40 ms (solid lines) and 4 patients had a postmexiletine QTc <500 ms.

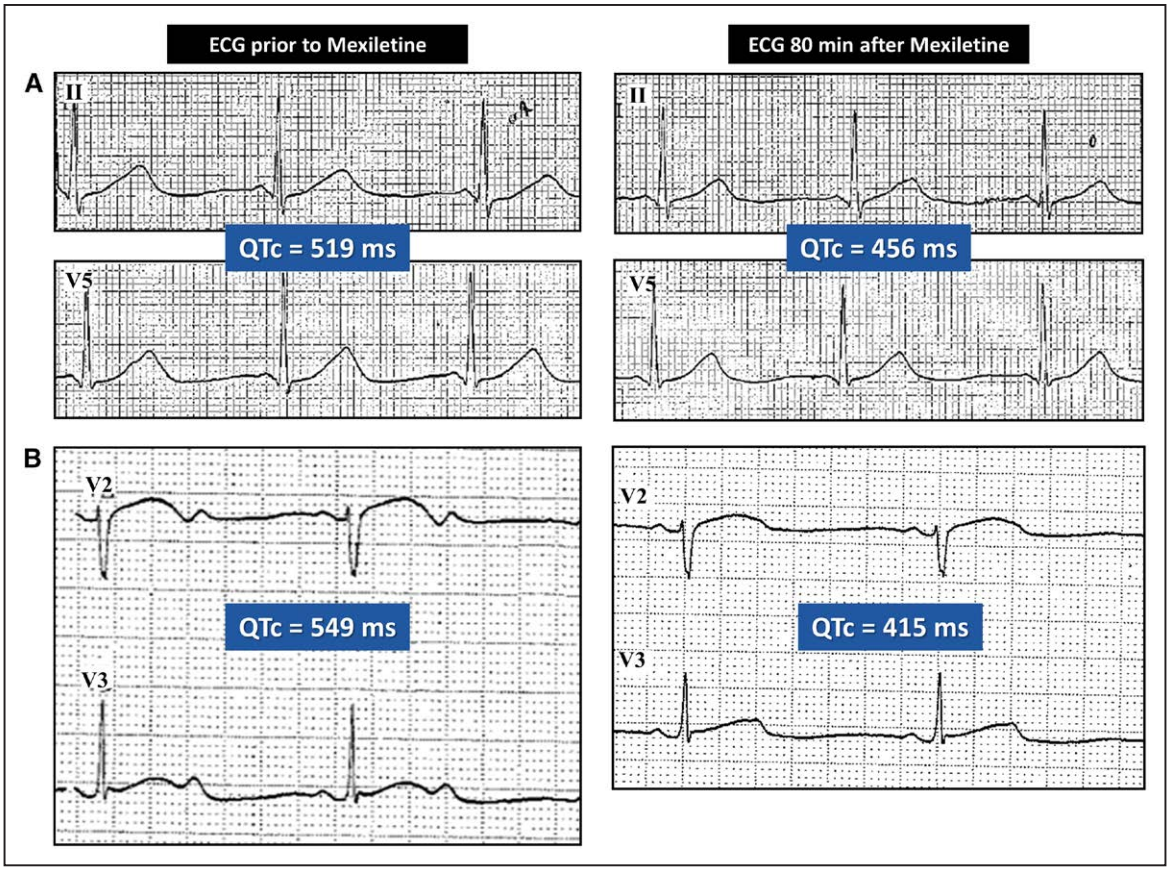

Figure 3. ECG example of mexiletine's acute effect on heart rate–corrected QT interval (QTc) in type 2 long QT syndrome.
A, Example of significant shortening effect on the QTc of a male patient (case 1) and (**B**) female patient (case 6) showing significant decrease of QTc within 80 min of mexiletine administration. Additional 12-lead ECGs before and after mexiletine therapy are also provided for case 5 and case 7 in the in the Data Supplement.

diately proceeding to more aggressive therapies, such as an ICD. Nonetheless, a prospective or randomized study comparing standard therapy to standard therapy plus mexiletine should be considered to establish the precise role and therapeutic efficacy of mexiletine in higher risk LQT2 patients.

While in tragic cases leading to a sentinel event of sudden cardiac death, recent studies have shown that the cardiac event rate in patients with LQTS, once diagnosed and optimally treated, is extremely low and the lethal event rate is almost anecdotal.[25,26] Nevertheless, certain patients remain symptomatic despite optimal, guideline-indicated treatment (BBs, left-sided cardiac sympathetic denervation, and ICDs) suffering BCE's, and the search for new or adjuvant, potentially genotype-specific, therapies continues.[15,25–27]

Aside from genotype, several clinical parameters have been established to aid in risk stratification and management of LQTS. Among those, the QTc, and especially a QTc >500 ms, remains one of the strongest risk factors in predicting cardiac events with the risk of life-threatening arrhythmias rising significantly as the resting QTc value increases.[28,29] Additionally, Priori et al[29] demonstrated in 2003 that arrhythmic risk was higher for patients with either LQT2 or LQT3, respectively, compared with LQT1. However, since BCEs still occur, albeit rarely, in all patients with LQTS, and specifically in patients with LQT3, physicians have been using mexiletine, a class IB sodium channel blocker, which has been associated with both shortening of the QT interval, as well as a decrease of LQT3-associated arrhythmic events in selected patients.[18–21]

Here, we explored the possibility that mexiletine might also decrease the QTc in patients with LQT2 and thereby potentially reduce the risk of cardiac events in patients with LQT2. Previously, Shimizu and Antzelevitch[30] showed, in cellular models mimicking LQT2 and LQT3 via administration of d-sotalol and ATXII (neurotoxin 2), respectively, that mexiletine abbreviated the QT interval and APD90 (action potential duration at 90% repolarization) in both models (ATX [LQT3 model] > d-sotalol [LQT2 model]), as well as caused total suppression of spontaneous torsades de pointes. Furthermore, lidocaine—a class IB antiarrhythmic like mexiletine—has been useful in diagnosing LQTS, by shortening the QT interval and QT dispersion to a greater extent in patients with LQTS than normal controls.[24,31]

Although these studies showed that the effects of these drugs were more prominent in LQT3-associated models or patients, a potential role and mechanism

for the use of mexiletine in treating patients with LQT2 has been emerging. In a prospective trial studying the effect of mexiletine on drug-induced QT prolongation, Johannesen et al[32] showed that mexiletine, in fact, counteracts the effects hERG (the *Kv11.1* human Ether-à-go-go-related gene encoded by *KCNH2*, ie, the same channel implicated in LQT2 genetically) potassium channel blocking drugs, such as dofetilide and moxifloxacin. Among the 22 patients studied, mexiletine significantly reduced the drug-induced QT prolongation by almost 20 ms for patients receiving concomitant dofetilide.[32] Badri et al[33] observed a similar effect in patients with acquired LQTS secondary to various underlying causes, such as amiodarone, dofetilide, hypothyroidism, or stress-induced cardiomyopathy, some of which are hERG-mediated as well. Addition of mexiletine in these patients led to shortening of the QT interval and prevention of all recurrences of torsades de pointes. In recent cellular studies, El-Bizri et al[34] showed that a novel mexiletine-like late sodium (I_{NA})-blocker shortened the action potential duration, stabilized ventricular repolarization, and decreased the proarrhythmic potential in situations of decreased I_{Kr}–activity (like LQT2). Most recently, the specific mechanism of action of mexiletine in patients with LQT3 has been elucidated whereby mexiletine alters the conformation of the voltage sensor domain III of the sodium channel where many of the LQT3-causative variants reside.[35] However, when the sodium channel is intact, it is unclear whether these findings might apply to LQT2.[35, 36]

In all, these studies, combined with our early clinical experience with mexiletine-treated patients with LQT2, suggest that combination drug therapy with a BB (preferably nadolol or propranolol) and mexiletine might provide an important therapeutic strategy for LQT2 patients who are assessed to be at high risk of an LQT2-triggered cardiac event.

CONCLUSIONS

Although commonly prescribed in patients with LQT3, mexiletine also shortens the QT significantly in a selected subset of patients with LQT2. In patients with high-risk LQT2, pharmacological targeting of the physiological late sodium current with mexiletine may provide added therapeutic efficacy to β-blocker therapy.

ARTICLE INFORMATION

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Disclosures

Dr Ackerman is a consultant for Audentes Therapeutics, Boston Scientific, Gilead Sciences, Invitae, Medtronic, MyoKardia, and St Jude Medical. Dr Ackerman and Mayo Clinic have potential equity/royalty relationships (without remuneration to date) with AliveCor, Blue Ox Health, and StemoniX. However, none of these entities participated in this study. The other authors report no conflicts.

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