Mexiletine Prevents Recurrent Torsades de Pointes in Acquired Long QT Syndrome Refractory to Conventional Measures

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ABSTRACT

OBJECTIVES The purpose of this study was to examine the role of mexiletine, a late sodium current (I_{Na,L}) blocker, in acute termination of torsades de pointes (TdP) refractory to conventional therapy in acquired long QT syndromes (LQTS).

BACKGROUND Long QT interval can predispose to TdP and is therefore associated with significant mortality. Currently, there is no available pharmacotherapy to target directly the ionic basis of most LQTS for the acute termination of TdP. Earlier evidence highlighted the role of I_{Na,L} in the pathophysiology of long QT and TdP, particularly in patients with congenital LQTS.

METHODS Twelve patients with TdP caused by acquired LQTS were treated with mexiletine after failure of conventional treatment including discontinuation of QT-prolonging drugs, intravenous administration of magnesium, and correction of serum electrolyte abnormalities.

RESULTS No recurrence of TdP occurred within 2 h after initiation of treatment with mexiletine in all 12 patients. Macro T-wave alternans accompanied by QT prolongation, an electrocardiographic precursor of TdP that was seen in 3 patients, was also abolished by mexiletine. Treatment with mexiletine shortened the QTc interval from 599 ± 27 ms to 514 ± 16 ms (p = 0.001). The interval from the peak to the end of the T-wave (T_{p-e} interval) decreased from 145 ± 18 ms to 106 ± 9 ms (p = 0.005). The T_{p-e}/QT ratio decreased from 0.27 ± 0.02 to 0.23 ± 0.018 (p = 0.01). Mexiletine had no significant effect on QRS complex duration.

CONCLUSIONS I_{Na,L} blockade with mexiletine may be an effective treatment approach to terminate refractory TdP from several acquired causes of LQTS. (J Am Coll Cardiol EP 2015;1:315–22) © 2015 by the American College of Cardiology Foundation.

Torsades de pointes (TdP) is a polymorphic form of ventricular tachycardia seen in the setting of QT interval prolongation that was first described by Dessertenne in 1966 (1). Other electrocardiographic manifestations that accompany significant QT prolongation include macro T-wave alternans (TWA) (2). Since the first description, the list of acquired pathologic conditions that lead to QT prolongation and TdP has markedly expanded. TdP is caused by either congenital or acquired long QT syndromes (LQTS). Whereas prescription drugs account for the majority of cases of acquired LQTS (3), other causes include post-myocardial infarction QT prolongation (4), electrolyte disturbances (hypokalemia, hypomagnesemia, and hypocalcemia), takotsubo cardiomyopathy (5), pheochromocytoma (6), and intracranial bleeding (7).
First-line treatment approaches to TdP include removal of the offending causes, the use of intravenous magnesium, maintenance of high-normal serum potassium level, and avoidance of QT-prolonging agents. In some refractory cases, isoproterenol infusion or temporary transvenous ventricular pacing may be required to increase heart rate, thereby to shorten the QT interval (8,9).

TdP often occurs during bradycardia or after a long pause that exaggerates the QT interval prolongation (10,11). Additionally, bradycardia and pauses increase the period from the peak to the end of the T-wave (T_{p\text{-}e}) which represents transmural dispersion of repolarization, during which ventricular muscle cells are most vulnerable to TdP. Recent basic research has shown that late sodium current (I_{Na-L}) is the key current contributing to rate adaptation of ventricular repolarization (12,13). When I_{Na-L} is large, ventricular repolarization, which is represented by the QT interval on the surface electrocardiogram (ECG), exhibits more prominent rate dependence. Conversely, delayed ventricular repolarization, irrespective of its etiology, can amplify I_{Na-L} by slowing its inactivation and is associated with bradycardia or pause-dependent exacerbation of QT and T_{p\text{-}e} prolongation (12,14). Therefore, inhibition of I_{Na-L} could be a common pharmacotherapeutic target for termination and prevention of TdP in LQTS.

Mexiletine, a Class Ib antiarrhythmic drug, is a potent blocker of I_{Na-L} even at therapeutic plasma concentrations (IC50—half maximum inhibitory concentration—of I_{Na-L} by mexiletine is 17.6 ± 1.9 μmol/l) compared with its relatively weak effect on the fast sodium current (15,16). Mexiletine was shown in animal models to shorten drug-induced QT prolongation (17-19). Mexiletine also shortens QT interval in patients with congenital LQT3 caused by a gain-of-function mutation in I_{Na-L} (20) and is therefore recommended as an additional therapy to beta-blockers in this subset of patients (21). However, clinical information regarding the use of an I_{Na-L} blocker in acute termination of TdP in acquired cases of LQTS that are not necessarily related to an increase in I_{Na-L} is lacking.

Although ranolazine also blocks I_{Na-L}, it inhibits the rapidly activating delayed rectifier potassium (I_{Kr}) current and may prolong the QT interval, thus limiting the potential of its use in this subset of patients.

Therefore, we investigated the role of I_{Na-L} blockade with mexiletine in the acute termination of TdP in several patients with acquired causes of LQTS. The effect of mexiletine on TWA was also studied.

METHODS

From June 2011 to February 2015, 12 consecutive patients with TdP in acquired LQTS were treated with mexiletine after failure of conventional treatment including discontinuation of QT-prolonging drugs, intravenous administration of magnesium, and correction of serum electrolyte abnormalities. The study was compliant with the declaration of Helsinki and was conducted in accordance with the policies of the Institutional Review Board of Lankenau Medical Center (Wynnewood, Pennsylvania) and the First Teaching Hospital of Xi’An Jiaotong University (Xi’An, China). Patients were identified by review of electrophysiology consultations during the study period. In each case, a review of medical records and medication administration history was performed. The most probable reason for TdP was determined on the basis of case review by a team of 7 board certified electrophysiologists. Demographic, clinical, and electrocardiographic parameters were collected for all patients. A 12-lead ECG was obtained before and after the first dose of mexiletine and as needed. All inpatients were continuously monitored on telemetry (7-lead ECG monitoring system).

Patients who developed TdP received conventional treatment first that included discontinuation of QT-prolonging agents or removal of the offending causes, intravenous magnesium, as well as replenishment of serum magnesium (target: 2 to 3 mg/dl), potassium (target: 4 to 5 mEq/l), and calcium (target: 9 to 10 mg/dl). Intravenous isoproterenol infusion or temporary transvenous pacing was also used in some cases of pause-dependent TdP. Mexiletine (200 to 450 mg/day orally) was administered to the patients with refractory TdP, defined as occurring at least 2 h after the administration of conventional therapy.

Study endpoints were as follows:

1. Treatment failure: Treatment with mexiletine was considered a failure if a patient had any episode of TdP more than 2 h after the first dose of mexiletine because the drug reaches peak plasma concentration 2 to 4 h after oral administration (22). TdP was defined as polymorphic ventricular tachycardia (≥3 beats) in the setting of QT prolongation. The treatment was also considered a failure if TWA persisted after treatment with mexiletine.

2. QTc interval, T_{p\text{-}e} intervals, and T_{p\text{-}e}/QT ratio: The QT interval in lead II/V5 or other leads with a clearly defined T-wave end were selected for measurement. The QTc interval was calculated using Bazett’s formula. The T_{p\text{-}e} interval was measured from the peak of the T-wave to the point where the steepest
down-slope of T-wave intersected the isoelectric line. The QT and $T_{p-e}$ intervals were measured manually on 3 consecutive beats without preceding ectopic beats, and the mean of 3 values was reported.

3. QT-RR relationship: The QT interval was measured using telemetry-monitored rhythms, and the pre-mexiletine and post-mexiletine QT-RR pairs were plotted for calculation of the slope for each individual patient who exhibited good-quality telemetry rhythm strips. A total of 112 pre-mexiletine QT-RR pairs and 118 post-mexiletine QT-RR pairs were obtained in 8 of 12 patients.

**RESULTS**

**STATISTICAL ANALYSIS.** All variables were expressed as mean ± SEM. Changes in the pre- and post-mexiletine QTc interval, $T_{p-e}$ interval, and $T_{p-e}/QT$ ratio were compared with 2-sided, paired $t$ tests. The pre-mexiletine and post-mexiletine slope of the QT-RR was calculated on the basis of the linear regression in each individual patient. The statistical analysis was performed between mean values of the slopes using the paired $t$ test.

**RESULTS**

Twelve patients (8 female) developed refractory TdP secondary to acquired QT prolongation. Recurrent TdP was present at least 2 h following conventional treatment including discontinuation of QT-prolonging drugs and correction of the offending causes, intravenous administration of magnesium, and correction of serum electrolyte abnormalities. Among these 12 patients, 3 patients had macro TWA. Causes of QT prolongation were drug-induced conditions, stress-induced cardiomyopathy, and severe hypothyroidism. Baseline characteristics, proposed causes of QT prolongation and TdP, arrhythmic manifestation, and description of TdP are listed in **Table 1**. Among the 12 patients, 2 patients had TdP refractory to intravenous isoproterenol infusion, and a third patient’s condition was refractory to temporary transvenous pacing. These 12 patients were then treated with oral mexiletine, 150 to 450 mg/day orally.

**EFFECTS OF MEXILETINE ON ACUTE TERMINATION OF TORSADES DE POINTES.** No further episodes of TdP occurred after 2 h following the first dose of mexiletine in all 12 patients. This antiarrhythmic effect was accompanied by resolution of frequent R-on-T ectopic beats ($n = 4$) and TWA ($n = 3$) (**Figure 1**). Three patients had nonsustained TdP within the first hour after mexiletine administration.

**EFFECTS OF MEXILETINE ON QTc, Tp-e INTERVALS, Tp-e/QT RATIO, AND QRS DURATION.** Mexiletine shortened the QTc interval from $599 ± 27$ ms to $514 ± 16$ ms ($p = 0.001$). The $T_{p-e}$ interval decreased from $145 ± 18$ ms to $106 ± 9$ ms ($p < 0.01$). The $T_{p-e}/QT$ ratio decreased from $0.27 ± 0.02$ to $0.23 ± 0.01$ ($p = 0.01$). Four examples of this effect are displayed in **Figure 2**.

**Table 1** Baseline Patient Characteristics, Proposed Causes of Long QT, Pre- and Post-Mexiletine QTc, $T_{p-e}/QT$ Ratio, Dose of Mexiletine Used, and Description of TdP

<table>
<thead>
<tr>
<th>Patient #</th>
<th>Age (yrs)/Sex</th>
<th>Proposed Cause(s) of Long QT</th>
<th>Baseline QTc (ms)</th>
<th>Pre-mexiletine $T_{p-e}/QT$</th>
<th>Mexiletine Dose</th>
<th>Post-Mexiletine QTc (ms)</th>
<th>Post-mexiletine $T_{p-e}/QT$</th>
<th>Delta QTc (ms)</th>
<th>Description of TdP</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>81/F</td>
<td>Stress-induced cardiomyopathy, amiodarone</td>
<td>810</td>
<td>0.378</td>
<td>200 mg bid</td>
<td>552</td>
<td>0.291</td>
<td>258</td>
<td>More than 5 runs of 10-15 beats for 48 h</td>
</tr>
<tr>
<td>2</td>
<td>73/F</td>
<td>Amiodarone</td>
<td>700</td>
<td>0.18</td>
<td>150 mg bid</td>
<td>590</td>
<td>0.2</td>
<td>110</td>
<td>More than 5 runs of up to 7 s</td>
</tr>
<tr>
<td>3</td>
<td>58/F</td>
<td>Amiodarone</td>
<td>480</td>
<td>0.21</td>
<td>150 mg bid</td>
<td>430</td>
<td>0.16</td>
<td>50</td>
<td>More than 5 runs of up to 25 beats</td>
</tr>
<tr>
<td>4</td>
<td>76/F</td>
<td>Amiodarone ± Levofloxacin</td>
<td>520</td>
<td>0.26</td>
<td>150 mg bid</td>
<td>500</td>
<td>0.23</td>
<td>20</td>
<td>More than 5 runs</td>
</tr>
<tr>
<td>5</td>
<td>66/M</td>
<td>Amiodarone ± Levofloxacin</td>
<td>610</td>
<td>0.26</td>
<td>150 mg bid</td>
<td>540</td>
<td>0.25</td>
<td>70</td>
<td>6 episodes of sustained TdP causing ICD shocks</td>
</tr>
<tr>
<td>6</td>
<td>85/F</td>
<td>Dofetilide</td>
<td>600</td>
<td>0.43</td>
<td>150 mg bid</td>
<td>460</td>
<td>0.3</td>
<td>140</td>
<td>More than 5 runs of TdP lasting 2-3 s</td>
</tr>
<tr>
<td>7</td>
<td>63/M</td>
<td>Dofetilide</td>
<td>489</td>
<td>0.22</td>
<td>200 mg once</td>
<td>446</td>
<td>0.18</td>
<td>43</td>
<td>More than 5 runs of TdP lasting 2-3 s</td>
</tr>
<tr>
<td>8</td>
<td>74/F</td>
<td>Dofetilide</td>
<td>509</td>
<td>0.161</td>
<td>150 mg bid</td>
<td>482</td>
<td>0.165</td>
<td>27</td>
<td>More than 5 runs of TdP lasting 2-3 s</td>
</tr>
<tr>
<td>9</td>
<td>72/M</td>
<td>Dofetilide, Severe hypothyroidism</td>
<td>650</td>
<td>0.2</td>
<td>150 mg bid</td>
<td>620</td>
<td>0.17</td>
<td>30</td>
<td>More than 5 runs of TdP lasting 2-3 s</td>
</tr>
<tr>
<td>10</td>
<td>49/F</td>
<td>Severe hypothyroidism</td>
<td>590</td>
<td>0.45</td>
<td>150 mg bid</td>
<td>520</td>
<td>0.28</td>
<td>70</td>
<td>10 episodes of sustained TdP despite temporary pacing</td>
</tr>
<tr>
<td>11</td>
<td>53/M</td>
<td>Unidentified</td>
<td>610</td>
<td>0.26</td>
<td>150 mg bid</td>
<td>530</td>
<td>0.18</td>
<td>80</td>
<td>2 sustained TdP episodes requiring defibrillation in addition to multiple short runs</td>
</tr>
<tr>
<td>12</td>
<td>66/F</td>
<td>Stress-induced cardiomyopathy</td>
<td>630</td>
<td>0.33</td>
<td>200 mg tid</td>
<td>500</td>
<td>0.34</td>
<td>130</td>
<td>Multiple sustained episodes of TdP</td>
</tr>
</tbody>
</table>

$bid$ = twice a day; ICD = implantable cardioverter-defibrillator; TdP = torsade de pointes; tid = 3 times a day; $T_{p-e}/QT$ ratio = ratio between the interval from the peak to the end of the T-wave and the QT interval.
Mexiletine exhibited no significant effect on QRS duration (105.1 ± 9 ms in pre-mexiletine vs. 105 ± 5.9 ms in post-mexiletine findings, p = 0.9).

**EFFECTS OF MEXILETINE ON QT-RR SLOPES.** TdP is often initiated after a characteristic short-long-short ventricular cycle sequence. As shown in Figure 3A, QT and Tp-e intervals were disproportionally prolonged after a longer RR interval (pause) that manifested as a larger T-wave with an increased Tp-e interval and facilitated the development of a R-on-T ectopic beat capable of initiating TdP. Mexiletine blunted the change in the T-wave amplitude and Tp-e duration after the pause (Figure 3B).

The QT-RR slopes were generated by plotting 112 pre-mexiletine QT-RR pairs and 118 post-mexiletine QT-RR pairs in 8 patients for whom detailed telemetry tracings were available. In all 8 patients, mexiletine treatment led to significant blunting of QT-RR relationship slopes (Figures 3C and 3D).

**DISCUSSION**

Our results suggest that mexiletine may be an effective treatment for acute termination of TdP in several acquired causes of QT interval prolongation. Mexiletine shortened the QTc and Tp-e interval and abolished TWA. Additionally, it decreased the Tp-e/QT ratio and blunted the bradycardia-dependent prolongation of the QT and Tp-e interval to account for its antiarrhythmic efficacy. The proposed ionic mechanism of this antiarrhythmic property is blockade of Ina,L current.

Delayed ventricular repolarization facilitates L-type calcium current (I_{ca,L}) reactivation that leads to the development of early afterdepolarization (EAD) during action potential phases 2 and 3. This serves as the trigger for TdP (23,24). Factors decreasing the net repolarizing force can amplify intrinsic dispersion of ventricular repolarization as a result of preferential prolongation of the action potential in cells with baseline weak repolarization forces such as mid-myocardial M cells (25). Amplified dispersion of ventricular repolarization manifests an increased Tp-e and Tp-e/QT ratio on the ECG and serves as a re-entrant substrate for the development of TdP. QT prolongation is associated with an enhanced QT-RR relationship through enhancement of Ina,L (12). In other words, the QT and Tp-e intervals are prolonged more significantly during bradycardia or after a pause. In the presence of QT-prolonging agents, the enhanced QT-RR relationship is termed reverse-use dependence (14,26). This can explain why TdP is often bradycardia or pause dependent.

I_{na,L} is a small portion of the sodium current that exhibits a slow inactivation kinetic and remains active mainly during the action potential plateau phase. Pathophysiologically, an increase in I_{na,L} contributes to the arrhythmogenic milieu facilitating the development of TdP by the following mechanisms: 1) an increase in dispersion of repolarization in response to preferential prolongation in cells with
weak repolarization reserve such as M cells (27); 2) facilitation of the development of EADs (28,29); and 3) enhancement of the QT-RR relationship (12,14). Antiarrhythmic effects of \( I_{Na-L} \) blockade have been previously documented in animal experiments (28,30–32). Using canine left ventricular wedge preparation, Shimizu and Antzelevitch showed that in wedge models of LQTS1, LQTS2 (31), and LQTS3 (28,31), \( I_{Na-L} \) blockade by mexiletine was effective in abbreviating repolarization, decreasing dispersion of repolarization, suppressing EADs, and preventing TdP. Similarly, in canine models of chronic atrioventricular block, the \( I_{Na-L} \) blocker ranolazine effectively prevented induction of TdP by dofetilide (33). We recently showed that in a rabbit left ventricular wedge model of Timothy syndrome (\( I_{Ca-L} \) augmentation by BayK 8644), \( I_{Na-L} \) blockade by mexiletine conferred similar antiarrhythmic effects (15).

On the clinical side, use of oral mexiletine or ranolazine (a potent \( I_{Na-L} \) blocker) was largely limited to patients with genotype-confirmed LQTS2 who had a gain of function mutation in \( I_{Na-L} \) (20,34). Our current study expands that observation to the use of mexiletine in acquired LQTS resulting from different causes. It validates pre-clinical data that \( I_{Na-L} \) is amplified in QT prolongation regardless of the underlying causes, plays a central role in rate dependence of the QT interval, and is vital in the pathogenesis of TdP. The inhibitory effect of mexiletine on TdP in our present study occurred likely through inhibition of \( I_{Na-L} \) because it shortened the QT and \( T_{pe} \) intervals (2 important ECG repolarization parameters) without significantly changing the QRS duration (an index of depolarization). As shown in our study, the etiology of and predisposition to QT prolongation/TdP in our patient group is diverse and sometimes multifactorial, including stress-induced cardiomyopathy, severe hypothyroidism, and the use of cardiac and noncardiac drugs that prolong the QT interval.

More importantly, an enhanced \( I_{Na-L} \) appears to contribute to bradycardia and pause-dependent exaggeration of the QT and \( T_{pe} \) intervals in diverse clinical situations. This concept is supported by the finding that mexiletine blunted the QT-RR
relationship in the patients presented in this series (Figures 3C and 3D) and was uniformly effective in treating TWA and TdP. It should be emphasized that the QTc intervals still remained prolonged after the first dose of mexiletine, although these intervals were shortened. This finding indicates that the offending causes of QT prolongation were not completely corrected when mexiletine terminated TdP. It is known that it may take several weeks for QT prolongation in stress-induced cardiomyopathy to normalize (35). This further indicates that blockade of INa-L may be a potentially promising treatment for congenital LQTS in which the underlying causes cannot be removed. It also suggests that such a treatment with blockade of INa-L can be used in congenital LQTS that is not necessarily limited to LQT3 from a gain of function in INa-L. This suggestion is supported by a recent study showing that mexiletine is useful in the treatment of LQT8, in which the underlying mechanism is a gain of the function in L-type calcium current (15).

Ranolazine is also an INa-L blocker that has been shown to suppress TdP in animal experiments (33). The major reason that we chose mexiletine instead of ranolazine is that ranolazine also blocks IKr (36) and can prolong the QT interval in patients (37). Additionally, ranolazine was linked to QT prolongation and TdP in a recent case report (38). Lidocaine, another Class Ib agent that also blocks late INa-L (39), shortens the QT interval, and in some cases it was shown to be effective in treatment of long QT and TdP (40,41). However, mexiletine inhibits INa-L more selectively than does lidocaine. IC50 of mexiletine for INa-L is 17.6 μmol/l, which is close to its therapeutic plasma concentration (15), whereas IC50 of lidocaine is 89 μmol/l (39), significantly higher than its therapeutic plasma concentration (42). However, it would be important to compare the efficacy of lidocaine with that of mexiletine in future clinical studies because the intravenous administration route of lidocaine would be advantageous in critically ill patients.
STUDY LIMITATIONS. First, this study lacks a comparative treatment arm. However, all patients received conventional emergency treatment of long QT/TdP, and mexiletine was used only when conventional measures failed to resolve the arrhythmogenic abnormalities.

Second, it may be argued that where a reversible cause was identified, it was the withdrawal of offending agent and not initiation of therapy with mexiletine that led to the beneficial clinical endpoint. However, the antiarrhythmic effects were consistently seen shortly (within 2 h) after the first dose of mexiletine in cases where TdP was refractory to conventional treatment and well earlier than the time when withdrawal of offending agent would have been extant. In fact, there were 4 cases in which frequent episodes of TdP persisted for more than 24 h despite conventional therapy combined with intravenous isoproterenol infusion or transvenous temporary cardiac pacing. As in the other 8 cases, mexiletine terminated TdP within 2 h after initiation of mexiletine.

Third, although these findings support the use of mexiletine in acquired LQTS, the duration of treatment optimal for this therapeutic benefit remains unclear. In 1 patient of this series, TdP resolved and mexiletine terminated TdP within 2 h after initiation of mexiletine.

Further studies to elucidate the duration of therapy will need to be performed.

CONCLUSIONS

With reversal of the offending cause, electrolyte replacement, and watchful waiting, TdP resolves in the majority of cases. However, in cases refractory to those treatments, an additional therapeutic option may be mexiletine. Proof of this concept will require studies of considerably larger size and scope.

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