Ranolazine for Congenital Long-QT Syndrome Type III
Experimental and Long-Term Clinical Data

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Background—The basic defect in long-QT syndrome type III (LQT3) is an excessive inflow of sodium current during phase 3 of the action potential caused by mutations in the SCN5A gene. Most sodium channel blockers reduce the early (peak) and late components of the sodium current ($I_{Na}$ and $I_{NaL}$), but ranolazine preferentially reduces $I_{Nat}$. We, therefore, evaluated the effects of ranolazine in LQT3 caused by the $D1790G$ mutation in SCN5A.

Methods and Results—We performed an experimental study of ranolazine in TSA201 cells expressing the $D1790G$ mutation. In the experimental study, $I_{Nat}$ was significantly higher in $D1790G$ than in wild-type channels expressed in the TSA201 cells. Ranolazine exerted a concentration-dependent block of $I_{Nat}$ of the SCN5A-$D1790G$ channel without reducing peak $I_{Na}$ significantly. In the clinical study, among 8 patients with LQT3 and confirmed $D1790G$ mutation, ranolazine had no effects on the sinus rate or QRS width but shortened the QTc from 509±41 to 451±26 ms, a mean decrease of 56±52 ms (10.6%; $P=0.012$). The QT-shortening effect of ranolazine remained effective throughout the entire study period of 22.8±12.8 months. Ranolazine reduced the QTc at all heart rates but less so during extreme nocturnal bradycardia. A type I Brugada ECG was never noticed.

Conclusions—Ranolazine blocks $I_{Nat}$ in experimental models of LQT3 harboring the SCN5A-$D1790G$ mutation and shortened the QT interval of LQT3 patients.

Clinical Trial Registration—URL: https://clinicaltrials.gov; Unique identifier: NCT01728025.

Key Words: action potential | bradycardia | long-QT syndrome | ranolazine | torsade de pointes

The long-QT syndrome (LQTS) type III (LQT3) is the third most common variant of the congenital LQTS.1 LQT3 differs from the more common (LQT1 and LQT2) variants of LQTS by important clinical and electrophysiological characteristics: (1) Patients with LQT3 develop arrhythmias less often, but these are more likely to be lethal when they ultimately occur.2 (2) In contrast to LQT1 and LQT2 patients, who develop arrhythmias primarily during stress or sudden startling, patients with LQT3 typically develop arrhythmias at rest, often while asleep.3 (3) Experimental models of LQTS suggest that heart rate slowing is particularly arrhythmogenic in LQT3 and β-adrenergic stimulation (rather than β-blockade) is antiarrhythmic in LQT3.4,5 Consequently, clinicians are often reluctant to initiate β-blocker therapy in patients with LQT3 who are not protected from bradycardia by cardiac pacing.6,7

The basic electrophysiological defect in LQT3 is an excessive inflow of sodium current during phase 3 of the action potential caused by mutations in the SCN5A gene.1 Thus, sodium channel blockers, including lidocaine,8 mexiletine,9–11 and flecainide,12,13 have been tested in LQT3. Specifically, in a large family with LQT3 caused by the $D1790G$ mutation described in Israel,14 Benhorin et al12 demonstrated impressive QT-shortening effects with flecainide therapy. The enthusiasm to treat LQT3 patients with flecainide lessened, however, after reports of flecainide-induced Brugada pattern in patients with LQT3.15 Concern about this potentially proarrhythmic effect of flecainide in LQT3 increased when the same $D1790G$ mutation described by Benhorin et al in patients with LQT3 was recognized in patients with a spontaneous type I Brugada ECG in the absence of drug therapy.14,16

Ranolazine is a relatively new medication (approved for the treatment of angina pectoris) that has unique electrophysiological properties.17–20 As opposed to other sodium channel blockers, which reduce both the early (peak) and late components of the sodium current ($I_{Na}$ and $I_{NaL}$, respectively)
WHAT IS KNOWN

• The LQT3, the third most common type of long-QT syndrome, is because of mutations in the SCN5A gene resulting in excessive inflow of the late sodium current during phase 3 of the action potential.

• Most sodium channel blockers reduce the early (peak) and late components of the sodium current (I(Na) and I(NaL)), but ranolazine preferentially reduces I(NaL).

WHAT THE STUDY ADDS

• In an experimental study of ranolazine in TSA201 cells expressing the D1790G mutation in SCN5A, ranolazine exerted a concentration-dependence block of I(NaL) of the SCN5A-D1790G channel without reducing peak I(Na) significantly.

• In a clinical study of 8 patients with LQT3 and confirmed D1790G mutation, ranolazine had no effects on the sinus rate or QRS width but shortened the QTc by 56±52 ms (10.6%). The QT-shortening effect of ranolazine remained effective throughout the entire 2-year study period. Ranolazine reduced the QTc at all heart rates but less so during extreme nocturnal bradycardia.

during phases 0, 2, and 3 of the action potential, ranolazine preferentially reduces I(NaL)\(^{17,21-24}\) Indeed, in a short-term clinical study involving 5 patients with LQT3, intravenous ranolazine shortened the QT interval without widening the QRS complex\(^{25}\) Moreover, ranolazine reduces calcium overload of myocardial cells, which contributes to the triggering of LQT-mediated arrhythmias\(^{26}\). Based on the above, ranolazine is a particularly attractive candidate therapy for LQT3. We, therefore, performed the present experimental and clinical study that included long-term evaluation of ranolazine in high-risk patients with LQT3.

Methods

Functional Characteristics of SCN5A-D1790G Channels

Wild-type (WT) and mutant constructs were cloned into a pcDNA3.1 expression vector. The SCN5A-D1790G plasmid was a kind gift from Dr. R.S. Kass (NY, USA). Sodium channels were expressed in modified human embryonic kidney cell line (TSA201) as previously described\(^{27}\). Briefly, TSA201 cells were cotransfected with SCN5A (WT or D1790G) and SCN1B using the FuGENE6 method. In addition, CD8 cDNA was cotransfected as a reporter gene to visually identify transfected cells using Dynabeads (M-450 CD8 Dynal; Invitrogen, Carlsbad, CA). Cells were cultured in DMEM with 10% fetal bovine serum and 2 mmol/L glutamine at 5% CO\(_2\). The cells were grown on polylysine-coated 35-mm culture dishes and placed in a temperature-controlled chamber at 37 °C for 24 to 72 hours. The biophysical properties of WT and mutant channels were then evaluated at room temperature. Membrane currents were measured using whole-cell patch-clamp techniques for cardiac I(Na)\(^{28}\). All recordings were obtained using an Axopatch 200B amplifier equipped with a CV-201A head stage (Axon Instruments, San Francisco, CA). Macrosopic whole-cell I(Na) was recorded with bath solution containing the following (in mmol/L): 140 NaCl, 5 KCl, 1.8 CaCl\(_2\), 1 MgCl\(_2\), 2.8 Na acetate, 10 HEPES, and 10 glucose (pH 7.3 with NaOH). Tetraethylammonium chloride (5 mmol/L) was added to block tetraethylammonium-sensitive native currents. Five pipettes were fabricated from borosilicate glass capillaries (1.5 mm OD; Fisher Scientific, Pittsburgh, PA). They were pulled using a gravity puller (Model PP-89; Narishige Corp, Tokyo, Japan) to obtain resistances between 1 and 2 mol/L when filled with a solution containing (in mmol/L) the following: 5 NaCl, 5 KCl, 130 CsF, 1.0 MgCl2, 5 EGTA, and 10 HEPES (pH 7.2 with CsOH). Measurements were started 10 minutes after obtaining the whole-cell configuration to allow the current to stabilize. Currents were filtered with a 4-pole Bessel filter at 5 kHz and digitized at 50 kHz. Series resistance was electronically compensated at 75% to 85%. All patch-clamp data acquisition and analysis were performed using pCLAMP V10.0 (Axon Instruments, Foster City, CA), EXCEL 2010 (Microsoft, Redmond, WA), and ORIGIN 7.5 (Microcal Software, Northampton, MA). Late sodium channel current (I(NaL)) was measured at the end of a 300-ms depolarization from a holding potential of –120 mV to –20 mV as the TTX-sensitive current. The effect of ranolazine on I(NaL) was evaluated at concentrations of 3.0, 10.0, and 100.0 mmol/L. Ranolazine was dissolved in distilled water and freshly prepared as a stock of 10 mmol/L before each experiment.

Clinical Evaluation of Ranolazine

Patient Population

We approached carriers of the D1790G mutation described in Israel\(^{14}\), who had a history of LQTS-related symptoms or a QTc ≥2500 ms at baseline ECG or during nocturnal bradycardia (in Holter recordings). Eight patients agreed to participate in this prospective study. Ranolazine (ranexa; Gilead Science, Inc) was started at 500 mg BID and increased after 3 days to 1000 mg BID, a dose that was continued throughout the study.

Electrocardiographic Measurements

The following measurements were made before and after the initiation of ranolazine therapy (every day during the first week and then every 3 months). Sinus rate, PR interval, QRS interval, QT, and QTc were evaluated at rest (after 10 minutes supine), and during maximal QTc stretching\(^{28,30}\) and QT stunning\(^{11}\) in response to quick standing. Symptom-limited exercise tests were conducted with the precordial leads placed on the second, third, and fourth intercostal space to increase the ability to detect a type I Brugada pattern.\(^ {22}\)

We measured the QT interval when the sinus rate reached 100 beats/min, at maximal exercise, and every minute during the recovery period for 5 minutes.\(^ {33}\)

Finally, we performed 12-lead Holter recordings at baseline and at least twice a year to monitor for the presence of nocturnal type I Brugada ECG and to study the effects of ranolazine on the QT interval during nocturnal bradycardia; specifically, for each patient, we manually measured the QT interval and its preceding RR interval at 100 different points in time during the Holter recordings, with particular emphasis on steady, slow heart rates recorded at night. We, then, estimated the QTc for each heart-rate category using the Bazett formula\(^ {34}\) and also the Fridericia\(^ {35}\) and Framingham\(^ {36}\) formulas that tend to overcorrect the QTc to a lesser degree during bradycardia. For each 10-beats/min heart-rate range, we calculated the respective ΔQT (and ΔQTc), which is the difference between the QT (and QTc) measured before drug therapy and the QT (QTc) measured during ranolazine therapy for the specific heart-rate range.

Statistical Methods

Statistical significance of differences between unrelated variables was calculated using Mann–Whitney U test and between matched variables using a Wilcoxon rank-sum test. Correlations between HR
category and QT or QTc lowering were assessed using the Spearman rank correlation coefficient. All clinical data were analyzed using SPSS for Windows version 15.0 by IBM.

The Internal Review Board of the Tel Aviv Medical Center and the Israel Ministry of Health approved the study protocol, including the off-labeled use of ranolazine for LQT3. All participants provided informed consent. The drug manufacturer (Gilead Sciences, Inc) provided supplies of the study medication at no cost but provided no funding for the study and had no access to the study results.

**Results**

**Experimental Studies**

**Functional Characteristics of Ranolazine on SCN5A-D1790G Channels**

The magnitude of \( I_{Na} \) (expressed as a percentage of peak \( I_{Na} \)) was significantly higher in \( D1790G \) than in WT channels expressed in the TSA201 cells (1.22±0.44% for \( D1790G \), n=5; 0.14±0.02% for WT n=22; Figure 1B). Ranolazine exerted a concentration-dependent block of \( I_{NaL} \) of the \( SCN5A-D1790G \) channel (Figure 1A). The half maximal inhibitory concentration \( (IC_{50}) \) was 6.73±1.27 \( \mu \)mol/L (Figure 1C). Figure 1D shows the original traces of peak \( I_{Na} \) recorded before and after applying 10 \( \mu \)mol/L ranolazine. The normalized I-V relationship (Figure 1E) demonstrates that with the control state, peak \( I_{Na} \) was not significantly reduced with the drug. Peak \( I_{Na} \) amplitude at −35 mV was decreased by 10.6±9.8% after 10 \( \mu \)mol/L ranolazine (n=5; \( P=0.31; \) Figure 1F).

**Clinical Studies**

**Baseline Characteristics**

Eight patients (4 men and 4 women, aged 41±20 years, range 16–66 years) were enrolled in the study. Two patients already had an implanted ICD: a 24-year-old woman with recurrent syncope and documented torsade de pointes and a 66-year-old man with symptomatic sinus node dysfunction. Six patients (including the 2 patients with implanted ICD) had previously received flecainide and have been reported. Additional medications included aspirin and ramipril for hypertension (2 patients) and thyroid supplement hormones (1 patient). For the entire patient cohort, the baseline RR interval was 1105±130 ms, the mean QT was 535±48 ms, and the mean QTc 509±41 ms. The QTc at resting ECG was ≥500 ms in all but one patient, who had a QTc >500 ms during nocturnal bradycardia.

**Compliance With Study Medications**

Two female patients discontinued the study medication: patient 7 stopped after 1 month because of constipation and patient 1 stopped after 6 months because of pregnancy. A third (male) patient admitted temporary discontinuation of the study drug after missing one follow-up appointment and consequently running out of drug supplies. Compliance with drug therapy was otherwise excellent based on pill counting and stable QT intervals.

**Effects of Ranolazine on Resting ECG Parameters**

Ranolazine had no significant effects on the sinus rate or on the QRS width during repeated resting ECGs. After 1 week of therapy with ranolazine 1000 mg BID, the resting QTc shortened from 509±41 to 451±26 ms, a mean decrease of 56±52 ms (11%; \( P=0.012; \) Figure 2). After 6 months of therapy, the mean QTc during resting ECG was 455±15 ms, representing a mean decrease of 52±40 ms (9.9%; \( P=0.017 \)) from baseline. The QT-shortening effect of ranolazine remained effective throughout the entire study period of 22.8±12.8 months except for 3 patients in whom the QTc prolonged back to baseline values during drug discontinuation (Figure 2). At the time of last follow-up on therapy, the mean QTc was shorter than that of baseline by 50±38 ms (\( P=0.017 \)). The 3 patients who had a return of QTc to baseline values included 2 female patients who dropped out of the study (because of constipation or because of pregnancy) and 1 male patient who ran out of study medications for 10 days (Figure 2). Importantly, 87% (7 out of 8) had a QTc ≥500 ms at resting ECG before therapy, and this percentage dropped to zero during all follow-up visits while on therapy.

**Effects of Ranolazine on the QTc During Provocative Tests**

The QT-shortening effect of ranolazine on the maximal QT stretching and QT stunning in response to quick standing was consistent across all patients studied and throughout the study period. As shown in Table, ranolazine significantly shortened the QTc during maximal QT stretching, whereas the QT-shortening effects did not reach statistical significance during QT stunning, during exercise, or during recovery from exercise. No patient exhibited a type I Brugada ECG in any ECG, at rest, during exercise, during recovery from exercise, or during nocturnal bradycardia (as assessed by 12-lead Holter recordings).

**Effects of Ranolazine During Nocturnal Bradycardia**

As expected, in the absence of therapy, our LQT3 patients had a disproportionate QT prolongation during nocturnal bradycardia, leading to bizarre T-wave morphologies (Figures 3A, 3C, and 4A). Ranolazine partially prevented this nocturnal QT prolongation (Figures 3D and 4D). Ranolazine significantly decreased the QT at every heart-rate range, including during bradycardia (Figure 4A). However, the QT- and QTc-shortening effects of ranolazine lessened during sinus bradycardia (Figure 4A). The QT/RR points measured during nocturnal bradycardia for heart rate <40 beats per minute (mean heart rate 35±3 beats per minute) are important. Within this heart-rate category, the QT-shortening effects of ranolazine reached statistical significance for the uncorrected QT (\( P=0.01; \) Figure 4A and 4C) and for the corrected QT using the Fridericia and Framingham formulas (\( P=0.005 \) and \( P=0.010 \), respectively). However, the QT-shortening effects of ranolazine, when assessed by the Bazzet formula, reached statistical significance except for the <40 beats per minute and the 60 to 70 beats per minute subcategories (\( P=0.093 \) and \( P=0.063 \), respectively; Figure 4B).

The ΔQT showed a U-shaped curve (Spearman rank correlation coefficient \( \rho=0.333; \) \( P=0.420; \) Figure 4C), whereas the ΔQTc (with the Bazzett formula) demonstrated maximal
QTc-shortening effects by ranolazine during spontaneous sinus tachycardia but less QTc-shortening effects during nocturnal bradycardia (Spearman rank correlation coefficient \( \rho = 0.714; P = 0.047 \); Figure 4D). Importantly, although a QTc > 500 ms was never observed in any resting ECG recorded while on ranolazine therapy, this highly abnormal value was
seen in all patients at least once during nocturnal bradycardia while on ranolazine.

Interobserver Variability
The QTc values calculated by the 2 investigators were different (512.11±13 versus 519.69±42 for a total of 2089 QT/RR measurements in ECG and Holter recordings). Although this difference was of statistical significance ($P=0.002$), the absolute interobserver difference of 7 ms had limited impact on the averaged 50 ms QTc shortening attributed to ranolazine therapy. Moreover, each of the 2 investigators independently found that ranolazine significantly shortens the QT interval in our patient population (data not shown).

Follow-Up
Our patients have been followed up for 19.3 patient-years (28.8±7.7 months per patient). Follow-up on therapy (after censoring for drug discontinuation) was 15.2 patient-years (22.8±12.8 months per patient). There were no documented or suspected arrhythmias during follow-up. Adverse effects included constipation in 2 patients (leading to drug discontinuation in 1).

Discussion
LQT3 patients are unique among patients with congenital LQTS because their arrhythmic events tend to occur predominantly at rest (often during sleep), a clinical characteristic reflecting the bradycardia-dependent proarrhythmic effects of vagal stimulation in LQT3. Consequently, whereas β-blocker therapy is the mainstay of therapy in the more common types of LQTS, sodium channel blocker therapy with either mexiletine or flecainide is increasingly being used to treat patients with LQT3. We report the first long-term study of ranolazine (a more specific blocker of $I_{Na,L}$) for LQT3.

Table. Effects of Ranolazine on the QT Interval of LQT3 Patients During Provocative Tests

<table>
<thead>
<tr>
<th></th>
<th>Before Therapy (n=8)</th>
<th>Ranolazine 2000 mg/d (1 wk; n=8)</th>
<th>Ranolazine 2000 mg/d (Last Follow-Up*; n=8)</th>
</tr>
</thead>
<tbody>
<tr>
<td>QTc before therapy</td>
<td>509±41</td>
<td>452±26$^\dagger$</td>
<td>458±10$^\dagger$</td>
</tr>
<tr>
<td>QTc before therapy</td>
<td>96±18</td>
<td>104±20</td>
<td>106±22</td>
</tr>
<tr>
<td>QT at maximal QT stretching</td>
<td>536±32</td>
<td>483±24$^\dagger$</td>
<td>483±36$^\dagger$</td>
</tr>
<tr>
<td>QT at QT stunning</td>
<td>524±56</td>
<td>454±28</td>
<td>469±23</td>
</tr>
<tr>
<td>Exercise QTc during sinus rate 100/min</td>
<td>465±12</td>
<td>457±16</td>
<td>448±21</td>
</tr>
<tr>
<td>Exercise QTc at maximal exercise</td>
<td>446±50</td>
<td>435±48</td>
<td>435±37</td>
</tr>
<tr>
<td>Exercise QTc at 1-min recovery</td>
<td>449±103</td>
<td>404±35</td>
<td>436±18</td>
</tr>
<tr>
<td>Exercise QTc at 5-min recovery</td>
<td>465±36</td>
<td>451±31</td>
<td>458±19</td>
</tr>
</tbody>
</table>

All values are presented in milliseconds.

*Last follow-up denotes the last follow-up on therapy, that is, without the values recorded after discontinuation of ranolazine in 3 patients (see text).

$^\dagger P<0.05$ in comparison to values before therapy.

$^{\ddagger}P<0.005$ in comparison to values before therapy.
Main Findings

We first show in experimental expression studies that the SCN5A mutation D1790G is a gain-of-function mutation with ≈3-fold increased $I_{NaL}$ and demonstrate that ranolazine blocks this increased $I_{NaL}$ current in a concentration-dependent manner (Figure 1). At the concentration close to the IC$_{50}$ on $I_{NaL}$, ranolazine displayed little effect on peak $I_{Na}$, inferring increased safety of ranolazine for treating LQT3 cases, who are at risk for developing Brugada syndrome during sodium channel blocker therapy.15,16 We then demonstrate that ranolazine shortens the QT interval of D1790G carriers with LQT3 and show that the QT-shortening effect of ranolazine persisted during the entire 20 patient-year follow-up period. Importantly, the QT-shortening effect of ranolazine persisted during nocturnal bradycardia, albeit to a lesser degree than during faster heart rates (Figure 4).

Previous Studies

Experimental Studies

Previous studies have reported that flecainide, but not lidocaine, corrects the disease phenotype in D1790G carriers by abbreviating QTc.12 Further investigation revealed that the D1790G mutation confers a unique pharmacological response in expressed channels.37 Lidocaine and flecainide differ in the way they block the cardiac sodium channel. Lidocaine interacts preferentially with the inactivated state of the channel so that block does not require channel openings,38,39 whereas flecainide blocks the open state of the channel and does not depend on channels entering the inactivated state.39,40 An open-state block mechanism underlies the use-dependent blocking effect of flecainide on D1790G channels.41 Similar to flecainide, ranolazine is an open-state blocker that unbinds rapidly from the closed state of the sodium channel but is trapped when the channel is in the inactivated state.42 Flecainide and ranolazine both reduce peak $I_{Na}$ and $I_{NaL}$, but in the ventricular myocardium ranolazine more selectively blocks $I_{NaL}$, and this selective $I_{NaL}$ underlies the QTc shortening in D1790G carriers. The greater selectivity for $I_{NaL}$, rather than peak $I_{Na}$, makes ranolazine a better choice in this situation.

Clinical Studies

The long-term effects of sodium channel blockers in LQT3 have been reported for flecainide12 and mexiletine.15 Benhorin
et al\textsuperscript{12} recently updated their long-term experience with LQT3 patients (all carriers of the D1790G mutation) now including 30 patients treated with flecainide for 83±73 months (Benhorrin, personal communication). At the same time, Mazzanti et al\textsuperscript{11} expanded their original experience with mexiletine to 34 LQT3 patients (with various mutations) treated for a median of 3 years. The baseline QTc of the patients treated with flecainide or mexiletine was similar to the baseline QTc of our patients (blue columns in Figure 5); it is therefore possible to compare the effects of these 3 medications on the resting QTc. The QT-shortening effects of all 3 sodium channel blockers are comparable: 10% shortening for flecainide, 12% shortening for mexiletine,\textsuperscript{11} and 11% shortening for ranolazine in the present study (red columns in Figure 5). Any drug studies of LQT3 patients should focus on the drug effects during nocturnal sinus bradycardia because cardiac arrest events in LQT3 tend to occur at night, and it is reasonable to assume that these tragic events occur when the heart rate is slowest and the QT prolongation is maximal. Of note, during extreme nocturnal bradycardia, our patients had a mean uncorrected QT >700 ms (Figure 4A) with highly abnormal T-wave morphology suggesting impending Torsades de Pointes (Figure 3C). Detailed evaluation of the effects of sodium channel blockers on the maximal QT interval recorded during extreme nocturnal bradycardia is only available for ranolazine (Figure 4, present study) because previous studies only reported the effects of sodium channel blockers on the QTc of the resting ECG (flecainide\textsuperscript{12} and mexiletine\textsuperscript{11}) or on the mean nocturnal QTc (mexiletine\textsuperscript{11}). Ranolazine shortened the QT and QTc at practically all heart rates, but the degree of QT and QTc shortening (ie, the ΔQT and ΔQTc) lessened as the sinus rate slowed down to <50 beats per minute (Figures 4C and 4D). At slow
Results

 QTc values >500 ms (a value that when recorded during rest ECG correlates with persistent risk of symptomatic arrhythmic events during mexiletine therapy) were often observed in our patients during nocturnal bradycardia.

(3) Automatic analysis of T-wave morphology changes observed during ranolazine therapy was not performed; this is a potential avenue for future research.

Disclosures

Dr Belardinelli was Senior Vice President, Cardiovascular Therapeutics at Gilead Sciences, manufacturer of the study drug (ranolazine) that was used in the study. Dr Antzelevitch was also a consultant to Gilead Sciences, Inc, at the time of the study. The other authors report no conflicts.

Sources of Funding

The experimental part of the study was conducted with funding from National Institutes of Health grant HL47678 and a research grant from Gilead Sciences, Inc. The drug manufacturer (Gilead Sciences, Inc) provided supplies of the study medication at no cost but provided no funding for the clinical study and had no access to the study results.

References


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