A New Oral Therapy for Long QT Syndrome

Long-Term Oral Potassium Improves Repolarization in Patients With HERG Mutations

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OBJECTIVES

We sought to determine whether oral potassium supplementation safely increases serum K⁺ and results in sustained improvement of repolarization parameters in long QT syndrome type 2 (LQT2) subjects.

BACKGROUND

Mutations in HERG (LQT2), the gene encoding the rapid delayed rectifier K⁺ current IKr, account for a significant proportion of congenital long QT syndrome (LQTS). The magnitude of IKr is paradoxically increased by an increase in extracellular K⁺. We tested the hypothesis that long-term oral potassium supplementation results in a mild, sustainable increase in serum K⁺ that improves repolarization abnormalities in subjects with LQT2.

METHODS

After an initial evaluation consisting of electrocardiography, electrolytes, blood urea nitrogen, and creatinine, escalating doses of potassium chloride (KCl) and spironolactone were administered to eight subjects with six distinct HERG mutations. Medications were continued for four weeks, at which time, the final evaluation was undertaken. Beta-adrenergic blocking therapy was maintained.

RESULTS

The subjects ranged in age from 11 to 52 years. The average daily KCl and spironolactone dose was 3.3 ± 1.5 mEq/kg and 3.5 ± 1.2 mg/kg, respectively, and this regimen resulted in an increase in serum K⁺ from 4.0 ± 0.3 to 5.2 ± 0.3 mEq/l. There were no serious complications associated with therapy. The increase in serum K⁺ resulted in a decrease in the corrected QT interval from 526 ± 94 to 423 ± 36 ms (mean ± SD; lead V̇). Both QT dispersion and T-wave morphology improved in most subjects.

CONCLUSIONS

Long-term oral potassium administration increases serum K⁺ in patients with LQT2. This can be achieved safely and results in improvement in repolarization. Further studies are warranted to determine whether this will reduce the incidence of life-threatening events in LQTS patients. (J Am Coll Cardiol 2003;42:1777–82) © 2003 by the American College of Cardiology Foundation

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Spironolactone resulted in a sustained, mild increase in serum K\(^+\) from 4.0 \(\pm\) 0.3 to 5.2 \(\pm\) 0.3 mEq/l, with no adverse events. The increase in serum K\(^+\) was associated with a decrease in QTc from 526 \(\pm\) 94 to 423 \(\pm\) 36 ms (lead V\(_2\)). QT dispersion also improved in all eight subjects. This study underscores the potential benefit of potassium supplementation as a novel treatment strategy for LQTS. Our findings serve as the basis for a larger study powered to determine the effect of this therapy on the improvement in cardiac event rates.

### METHODS

The study was reviewed and approved by the University of Utah’s Institutional Review Board. Written, informed consent was obtained. We prospectively studied eight patients from six families with HERG mutations. No subject had structural heart disease. No changes were made in the study participant’s prior therapy while taking part in this protocol. Six subjects, including four children, were taking beta-blockers. One adult had a permanent atrial pacemaker in place due to intolerance of beta-blockers. A 52-year-old asymptomatic patient was not receiving therapy.

Baseline testing included an ECG, 24-h Holter monitor, exercise treadmill study (standard Bruce protocol), serum pregnancy test, serum electrolytes, blood urea nitrogen, and creatinine. After the baseline evaluation was completed, oral KCl and spironolactone therapy was initiated. The starting KCl dose was 1.5 mEq/kg (maximum starting dose 20 mEq) every 12 h and spironolactone 1.5 mg/kg (maximum dose 30 mg/kg) every 12 h. The KCl dose was increased by 0.5-mEq/kg increments alternating with 0.5-mg/kg increments in the dose of spironolactone every 48 to 72 h. The target serum K\(^+\) level was 1.5 mEq/l above baseline. Serum electrolytes, blood urea nitrogen, and creatinine levels were obtained every 48 to 72 h and before increases in the medication dose. Once the target serum K\(^+\) level was reached and maintained at steady-state for three consecutive determinations over a six- to nine-day period, the frequency of blood testing was decreased to weekly for the four-week maintenance period. At the conclusion of the four-week maintenance phase of the study, the blood tests and ECG were repeated.

The ECGs were analyzed manually in a blinded fashion. The QT interval was defined as the intersection of a tangent to the steepest down-slope of the dominant repolarization wave with the isoelectric baseline. The T waves were rated as biphasic when two distinct components of opposite polarity were present. The T-wave morphology was rated as notched when a second positive deflection interrupted the descending phase of the T wave. QT dispersion was defined as the difference between the longest and shortest QT interval (11) and was measured in a minimum of eight ECG leads.

Statistical analysis was performed using the Student two-tailed \(t\) test (SigmaStat version 2.03, SPSS Inc., Chicago, Illinois) and a linear mixed model analysis (S-Plus version 6.0, Insightful, Seattle, Washington). A \(p\) value <0.05 was required for statistical significance. Data are presented as the mean \(\pm\) SD.

### RESULTS

Table 1 describes the HERG nucleotide substitution, coding effect, and functional effect of the mutation in the eight subjects. Figure 1 depicts the location of the mutations.

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Nucleotide Change</th>
<th>Coding Effect</th>
<th>Location</th>
<th>Functional Effect</th>
<th>Reference</th>
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<td>G572C</td>
<td>S5</td>
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<td>N470D</td>
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</tr>
<tr>
<td>3</td>
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<td>E682X</td>
<td>C-terminus</td>
<td>Unknown</td>
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<td>4</td>
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<td>A561T</td>
<td>S5</td>
<td>Trafficking defect*</td>
<td>21,22*</td>
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<td>5</td>
<td>C1844T</td>
<td>A614V</td>
<td>Pore helix</td>
<td>Dominant-negative effect, altered inactivation</td>
<td>23</td>
</tr>
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<td>A561T</td>
<td>S5</td>
<td>Trafficking defect*</td>
<td>21,22*</td>
</tr>
<tr>
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<td>C3040T</td>
<td>R1014X</td>
<td>C-terminus</td>
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<td>24</td>
</tr>
<tr>
<td>8</td>
<td>C3040T</td>
<td>R1014X</td>
<td>C-terminus</td>
<td>Trafficking defect</td>
<td>24</td>
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</table>

*Trafficking defect described for a Val substitution at the same position (A561V). Subjects 4 and 6 are related family members, as are Subjects 7 and 8.
patients. The QT dispersion at baseline was 100
therapy (Table 3).
inity in the measured QTc, the degree of variability was less
obtained before therapy. Although there was some variabil-
model analysis) (Fig. 4). To assess QTc variability within
location of the mutation and the effect of QTc shortening
therapy). There was no apparent correlation between the
resting QTc in all subjects (Fig. 2). The three subjects with
the longest QTc experienced the greatest reduction in QTc
(Patient 2: 684 to 496 ms; Patient 5: 638 to 441 ms; and
Patient 7, 560 to 408 ms in QTc lead V2 before and after
therapy was well tolerated without signiﬁcant side effects.
One subject complained of mild muscle cramps, and an-
other experienced orthostatic dizziness that improved with
increased ﬂuid intake. Renal function measurements re-
mained stable throughout the trial.
An increase in serum K+ resulted in a decrease in the
resting QTc in all subjects (Fig. 2). The three subjects with
the longest QTc experienced the greatest reduction in QTc
(Patient 2: 684 to 496 ms; Patient 5: 638 to 441 ms; and
Patient 7, 560 to 408 ms in QTc lead V2 before and after
therapy). There was no apparent correlation between the
location of the mutation and the effect of QTc shortening
(Table 1, Fig. 2). The mean QTc, as measured in leads II,
V2, and V4, was signiﬁcantly reduced after therapy with KCl
and spironolactone (Fig. 3). For 81 ECG recordings and
other experienced orthostatic dizziness that improved with
increased ﬂuid intake. Renal function measurements re-
mained stable throughout the trial.

Table 2. Patient Demographic Data

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Age (yrs)</th>
<th>Weight (kg)</th>
<th>Previous Therapy</th>
<th>Baseline QTc in Lead II (ms)</th>
<th>Final QTc in Lead II (ms)</th>
<th>Final K+ (mEq/l)</th>
<th>Final K+ (mg/kg)</th>
<th>Dose KCl (mEq/kg)</th>
<th>Final K+ (mEq/l)</th>
<th>HR After Therapy (beats/min)</th>
<th>HR Before Therapy (beats/min)</th>
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<td>2.2</td>
<td>3.5</td>
<td>3.5</td>
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</table>

Mean ± SD: 49.2 ± 69.0

*Patients 4 and 5 and Patients 7 and 8 are related family members.
†Atrial paced subject.
‡BB = beta-blocker; HR = heart rate; K+ = serum potassium; PM = pacemaker; QTc = corrected QT interval.

**DISCUSSION**

The application of molecular genetics to cardiovascular
disease has allowed the identiﬁcation of mutations in ion
channel genes as the cause of LQTS. The speciﬁc genotype
inﬂuences the characteristics of the clinical phenotype,
including the arrhythmia trigger, frequency of life-
threatening events, and T-wave morphology (12–14). The
discovery of a distinct molecular basis for LQTS has fostered a hope for speciﬁc therapy directed at the gene
defect.
The rationale for the current study is based on the observation that the I_Kr magnitude increases paradoxically with increased extracellular K+ (11), that is, despite a decrease in the chemical driving force. We hypothesized that increasing serum K+ within the physiologic range would augment the repolarizing current and result in improvements in repolarization parameters in individuals with HERG mutations.

We previously reported that an early increase in serum K+ achieved by intravenous KCl reduced the QTc interval by 24% and improved repolarization parameters in LQT2 subjects (10). The current study demonstrates that a sustainable, mild increase in serum K+ can be safely maintained by oral potassium supplementation and spironolactone. The increase in serum K+ was associated with a significant reduction in QTc and QT dispersion in all subjects, as well as normalization of the T-wave morphology in one-half of the subjects. A dramatic decrease in QTc with elevated serum K+ was observed in three individuals. The improvement in repolarization parameters achieved in this study suggests that oral KCl and spironolactone may be effective adjunctive therapy, together with beta-blockers, for the treatment of LQTS.

The precise mechanism whereby an increase in serum K+ results in shortening of the QT interval in study patients is not known. The primary mechanism of HERG channel sensitivity to extracellular K+ is relief of the channel block by extracellular Na+ (15,16). Additionally, increased extracellular K+ induces a depolarizing shift in the voltage

![Figure 2](image1.png)  
**Figure 2.** The individual response of the corrected QT interval (QTc) to increased serum K+ in long QT syndrome type 2 (LQT2) subjects. Scatter plot of QTc intervals measured in lead V2 at baseline and after a four-week course of oral KCl and spironolactone. An increase in serum K+ from 4.0 ± 0.3 at baseline to 5.2 ± 0.3 mEq/l resulted in a decrease in QTc in all subjects.

![Figure 3](image2.png)  
**Figure 3.** The mean corrected QT interval (QTc) shortens in response to an elevation in serum K+. Graphic demonstration of the mean QTc intervals measured in ECG leads II, V2, and V4 at baseline and after increasing the serum K+ level with oral KCl and spironolactone. The treatment protocol was associated with a statistically significant decrease in QTc (p value = 0.002, 0.003, and 0.003 for leads II, V2, and V4, respectively, using the paired t test).

![Figure 4](image3.png)  
**Figure 4.** Relationship between individual serum K+ measurement and corrected QT interval (QTc). Scatter plot demonstrating a negative correlation between the QTc interval and serum K+ level from eight study patients (total of 81 determinations). Individual symbols represent a single study patient (Fig. 2). (r = −0.52, p < 0.0001 by linear mixed model analysis). The ECGs and serum electrolytes were obtained on the same day.
dependence of HERG channel inactivation, resulting in an increase in channel availability (17,18). Either of these two mechanisms might increase the current magnitude through homomultimeric wild-type HERG channels or heteromultimeric channels formed by wild-type and mutant subunits. The observation that HERG-specific T-wave dysmorphisms were normalized in some subjects suggests that I_{Kr} was specifically increased. Alternatively, the increase in the repolarizing current may be due to an increased magnitude of the inward rectifier K^{+} current, I_{K1}, which is also paradoxically sensitive to increased extracellular K^{+} (19). This hypothesis is more appealing given that the majority of the mutations cause a dominant-negative effect (Table 1).

Table 3. Corrected QT Interval Variability (Lead V_{2}) on Pre-Treatment Electrocardiograms

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>n*</th>
<th>Mean QTc (ms)</th>
<th>SD</th>
<th>CI of Mean</th>
<th>ΔQTc With KCl Therapy (ms)</th>
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<tr>
<td>1</td>
<td>2</td>
<td>521</td>
<td>1.4</td>
<td>12.7</td>
<td>74</td>
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<tr>
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<td>3</td>
<td>655</td>
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<tr>
<td>3</td>
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<td>455</td>
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<td>52</td>
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<td>451</td>
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<td>453</td>
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<td>10.3</td>
<td>68</td>
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*Number of ECGs available before enrollment.
CI = 95% confidence interval; ΔQTc = change in corrected QT interval; SD = standard deviation.

Figure 5. The effect of elevated serum K^{+} on T-wave morphology. Representative ECG tracings from study Patients 2, 4, 5, and 6, showing the improvements in repolarization and T-wave morphology after increasing serum K^{+}. Values represent serum K^{+} levels at baseline and after four weeks of KCl and spironolactone therapy.
(20–24). It is unlikely that the improvement in repolarization parameters was due to a direct effect of spironolactone, given that spironolactone derivatives prolong the action potential duration in isolated cardiac preparations (25). However, we cannot exclude an indirect effect of aldosterone blockade on myocellular repolarization. Finally, increased serum potassium may exert secondary effects on other ion channels critical in modulating the cardiac action potential duration by altering the resting membrane potential of cardiomyocytes.

**Study limitations.** This is a small series with a relatively short-term duration of therapy and follow-up. Although the QTc was significantly shortened by treatment with oral potassium supplementation, it remains to be proven that changes in the QTc duration will translate into a decreased risk of symptoms or sudden cardiac death. It is also unclear whether the observed increase in serum K+ is sustainable over the long run, without significant side effects. Although the side effects of therapy were minimal, the long-term safety and efficacy of oral KC1 and spironolactone remain to be determined. Gynecomastia, a well-characterized side effect of high-dose spironolactone therapy, was not seen in our subjects, but may emerge as an important complication with prolonged therapy.

The results of the study must also be interpreted with caution, given the small sample size. Larger studies of greater duration are currently in progress to address the question of a long-term benefit of KCl therapy in LQTS.

**Clinical implications.** Irrespective of the specific current that is modulated by extracellular K+, an increase in serum K+ would be predicted to shorten repolarization in other forms of inherited LQTS. In fact, one could argue that the effect of increased serum K+ may be greater in KCNQ1 and SCN5A subjects due to the presence of fully functional HERG channels. In contrast, mexiletine is effective in shortening the QT interval only in individuals with mutations in SCN5A (LQT3), presumably by blocking the abnormally sustained plateau Na+ current (26). Whether increasing serum K+ proves to be effective in improving repolarization parameters in other forms of LQTS is currently under investigation.

**Acknowledgments**

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