Complexity of ranolazine and phenytoin use in an infant with long QT syndrome type 3

Reina Bianca Tan, MD, Sujata Chakravarti, MD, Melissa Busovsky-McNeal, MD, Abigail Walsh, NP, Frank Cecchin, MD

From the Division of Pediatric Cardiology, New York University Langone Medical Center, New York, New York.

Introduction
Long QT syndrome type 3 (LQT3) results from gain-of-function mutations in the \( SCN5A \) gene, which encodes the major cardiac sodium channel, voltage-gated type V alpha subunit (NaV 1.5). Those mutations result in an increase in late sodium channel current, which leads to delayed ventricular repolarization, torsades de pointes (TdP), and sudden death.

Traditionally, beta-blockers mexiletine and phenytoin have been the agents of choice in the management of LQT3. Ranolazine is a novel antianginal drug that has been shown to have multichannel blocking effects, including the late sodium channel current (\( I_{Na,L} \)) and the rapid delayed-rectifier potassium current (\( I_{Kr} \)). The extended-release formulation of ranolazine has a half-life of 7 hours. It has been used in adults with LQT3 \(^1\); however, there are currently no published data on its use in the pediatric population. Data have shown that ranolazine is more effective in inhibiting the late vs the peak Na\(^+\) current in LQT3 caused by \( SCN5A \) mutations. We theorize that use of ranolazine in an infant with LQT3 and persistent TdP refractory to multiple medications would be effective. We report that ranolazine use in infants is very difficult and found that phenytoin was the most effective agent in our patient.

Case report
A full-term female infant was delivered by emergency caesarean section owing to fetal bradycardia. Initial cardiac assessment revealed 2:1 atrioventricular block (atrial rate 120 and ventricular rate 60) and corrected QT of 690 milliseconds (Figure 1) with short episodes of TdP. Echocardiogram showed severely depressed left ventricular function with otherwise normal intracardiac anatomy. There was no family history of sudden death or long QT syndrome and both parents had normal electrocardiograms.

Genetic testing identified an SCN5A c.A4424C variant resulting in p.Q1475P missense mutation in the Na\(_{\text{v}}\)1.5 inactivation gate (DIII/DIV, interlinker domain). In addition, a KCNH2, c.A2690C, p.K897T polymorphism was detected, the gene coding for the hERG potassium channel (\( I_{Ks} \)). No mutations were identified in KCNQ1, KCNE1, and KCNE2.

The patient was initially treated with isoproterenol, magnesium, and propranolol; however, episodes of TdP persisted. The sodium channel blocker mexiletine was added, followed by flecainide. However, QTc remained prolonged, with T-wave alternans and TdP. As the flecainide was increased there was widening of the QRS duration, so it was discontinued. She then underwent epicardial dual-chamber implantable cardioverter-defibrillator / pacemaker implantation in combination with a left cardiac sympathetic denervation. AAII pacing to augment heart rate led to 2:1 atrioventricular block and VVI pacing increased episodes of TdP. Ultimately she was left on backup AAII pacing at 100 beats per minute. Episodes of TdP persisted, so ranolazine was started. Initially a low dose (2–25 mg/kg/day, every 12 hours) was used, but the plasma trough level was low. The dose was increased and the dosing interval decreased (50 mg/kg/day, every 6 hours), with a reduction in episodes of TdP, though the QTc remained prolonged with frequent T-wave alternans. She was discharged home at 2.5 months of age on propranolol 3 mg/kg/day every 6 hours, mexiletine 30 mg/kg/day every 8 hours, and ranolazine 50 mg/kg/day every 6 hours. After discharge, she had multiple episodes of TdP, 2 of which required defibrillation despite a maximal ventricular fibrillation detection interval of 30 seconds. The ranolazine dose was increased to 60 mg/kg/day, with levels showing appropriate peak levels but still with low trough levels.

At 1 year of age, she was noted again to have frequent episodes of TdP, 1 of which required defibrillation. This occurred just before a scheduled dose of ranolazine. In addition, T-wave alternans was still present. After review of prior ranolazine levels and knowing that the elimination half-life was 1.4–1.9 hours, it became clear that in order to...
increase the trough level, dosing would have to be changed to every 4 hours. This was not practical on a long-term basis, so we chose to try and boost the trough level by adding a cytochrome P450 (CYP) 3A inhibitor, as ranolazine is metabolized by the CYP3A enzyme system. The CYP3A inhibitor verapamil was chosen. Verapamil was started at 4 mg/kg/day divided over every 8 hours. The ranolazine level obtained showed increased trough and peak levels, but the patient developed increasing episodes of TdP, which we attributed to high-affinity block of hERG by verapamil (Table 1). She subsequently had a prolonged admission owing to frequent arrhythmia storms. She had multiple daily episodes of TdP that were managed with cardiopulmonary resuscitation to avoid frequent defibrillation and weekly storm events requiring defibrillation. Verapamil was discontinued and diltiazem, a CYP3A inhibitor that weakly blocks hERG, was started. She continued to have arrhythmia storms with high levels of ranolazine, suggesting possible proarrhythmia at elevated levels, so the ranolazine dose was decreased. Phenytoin, a third sodium channel blocker, was initiated. At lower levels of ranolazine with therapeutic mexiletine and phenytoin levels, arrhythmia control was achieved. This admission was complicated by seizures, likely owing to elevated mexiletine levels. Mexiletine dose was decreased and she was later placed on anti-seizure medications levetiracetam and topiramate. The addition of phenytoin occurred after seizure control had been achieved.

With a regimen of ranolazine, mexiletine, phenytoin, diltiazem, and propranolol, we have reduced the patient’s arrhythmia burden from >50 episodes per day to zero (Figure 2). After 6 months of control, ranolazine and diltiazem were discontinued, and there have been no TdP episodes in the last 2 months. She is currently on a regimen of mexiletine 10 mg/kg/dose every 8 hours, phenytoin 4 mg/kg/dose every 8 hours, and propranolol 1 mg/kg/dose every 8 hours. She continues to have prolonged QT with a QTc of 595 msec (Figure 3).

**Discussion**

To our knowledge, this is the first reported use of ranolazine in an infant with severe LQT3. We discovered the complexities of using ranolazine in infants, related to its short half-life as well as drug interactions. We also characterized the pharmacokinetics of ranolazine in infants and describe the use of a CYP3 inhibitor to extend the half-life. Finally, we found that phenytoin was more efficacious than ranolazine.
On the basis of T-wave morphology, a presumptive diagnosis of LQT3 was made and treatment with Na\(^+\) channel blockers and beta-blockers initiated. Genetic testing later confirmed the diagnosis with mutation in the inactivation gate of the sodium channel (p.Q1475P) as well as a polymorphism in hERG. Bankston et al\(^2\) reported a patient with a similar clinical history that had a missense mutation 2 amino acid residues away from our patient’s mutation in the inactivation gate of NaV1.5 (p.F1473C) and the same hERG polymorphism. Patch clamp testing of NaV1.5 (p.F1473C) function revealed marked increase in the late sodium channel current as well as faster recovery for inactivation, both contributing to delayed repolarization. Pharmacologic response of the mutant channel to different Na\(^+\) channel blockers was determined. Ranolazine, mexiletine, and flecainide all preferentially inhibited the late vs peak Na\(^+\) channel currents. However, ranolazine and mexiletine causes hyperpolarizing shifts in the voltage-dependent steady-state inactivation, which leads to restoration of closed-state inactivation, whereas flecainide displayed no such effect, making it an ineffective drug for this mutation.\(^2\) Similar clinical response was noted in our patient.

The polymorphism in KCNH2 (p.K897T) is common and has been extensively studied; however, data have been conflicting as to how it affects hERG channel function. Some studies have shown that although the mutation does not typically cause disease by itself, when combined with QT-prolonging drugs or coinheritance of a long QT syndrome mutation it may accentuate the effects of reduced repolarization reserve.\(^3,4\)

Ranolazine is a new antianginal drug with novel electrophysiologic properties and is known to inhibit a number of ion channel currents. However, ranolazine and mexiletine causes hyperpolarizing shifts in the voltage-dependent steady-state inactivation, which leads to restoration of closed-state inactivation, whereas flecainide displayed no such effect, making it an ineffective drug for this mutation.\(^2\) Similar clinical response was noted in our patient.

The polymorphism in KCNH2 (p.K897T) is common and has been extensively studied; however, data have been conflicting as to how it affects hERG channel function. Some studies have shown that although the mutation does not typically cause disease by itself, when combined with QT-prolonging drugs or coinheritance of a long QT syndrome mutation it may accentuate the effects of reduced repolarization reserve.\(^3,4\)

Ranolazine is a new antianginal drug with novel electrophysiologic properties and is known to inhibit a number of ion channel currents. However, ranolazine and mexiletine causes hyperpolarizing shifts in the voltage-dependent steady-state inactivation, which leads to restoration of closed-state inactivation, whereas flecainide displayed no such effect, making it an ineffective drug for this mutation.\(^2\) Similar clinical response was noted in our patient.

The polymorphism in KCNH2 (p.K897T) is common and has been extensively studied; however, data have been conflicting as to how it affects hERG channel function. Some studies have shown that although the mutation does not typically cause disease by itself, when combined with QT-prolonging drugs or coinheritance of a long QT syndrome mutation it may accentuate the effects of reduced repolarization reserve.\(^3,4\)

Ranolazine is a new antianginal drug with novel electrophysiologic properties and is known to inhibit a number of ion channel currents. However, ranolazine and mexiletine causes hyperpolarizing shifts in the voltage-dependent steady-state inactivation, which leads to restoration of closed-state inactivation, whereas flecainide displayed no such effect, making it an ineffective drug for this mutation.\(^2\) Similar clinical response was noted in our patient.

The polymorphism in KCNH2 (p.K897T) is common and has been extensively studied; however, data have been conflicting as to how it affects hERG channel function. Some studies have shown that although the mutation does not typically cause disease by itself, when combined with QT-prolonging drugs or coinheritance of a long QT syndrome mutation it may accentuate the effects of reduced repolarization reserve.\(^3,4\)
currents. In adult patients with LQT3, it has been shown to shorten the QTc interval in a concentration-dependent manner. In a study by Moss et al., QTc shortened at peak plasma concentrations between 908 and 2074 ng/mL; however, there were no data with higher concentration levels beyond the therapeutic concentration used for treatment of angina. Pharmacokinetics have been studied extensively in adults, with peak concentrations of immediate-release preparations noted 1 hour after oral administration. Elimination half-life is 1.4–1.9 hours for immediate-release preparations and 7 hours for extended-release preparations. Its bioavailability is 35%–50% and it is renally excreted and metabolized by CYP3A enzymes.

Dosing for the extended-release formulation is twice a day. For our patient, a suspension was made by crushing extended-release tablets and adding sterile water and Ora-Plus (Perrigo Australia; Perth, Australia). Dosing was initially extrapolated from adult dosing and then tailored based on drug levels and clinical response of the patient.

Because the metabolism of ranolazine was unknown in infants, we started dosing every 12 hours and were able to check plasma levels courtesy of Gilead Science. Initial levels obtained showed peak levels occurring at 1 hour, with the half-life (as estimated by earlier studies) at approximately 2 hours. Decreasing the dosing interval from every 12 hours to every 6 hours mildly increased trough levels while significantly increasing the peak levels. Because steady-state levels could not be obtained with the short-acting preparation, we decided to add a CYP3A inhibitor to increase the half-life and obtain higher trough levels. Our choice of CYP3A inhibitor was based on pharmacokinetic studies by Jerling and Gilead Science. Verapamil and diltiazem are CYP3A inhibitors that increase ranolazine exposure by 100% and 50%–130%, respectively. Both are also antagonists of the delayed-rectifier potassium current. In a study by Zhang et al., they showed that verapamil is a potent antagonist of the hERG channel, whereas diltiazem only weakly suppresses it. With the addition of verapamil, the initial levels showed appropriate trough and peak levels with clinically good control at that time. However, prolonged exposure to verapamil led to elevated steady-state levels that were beyond the peak plasma concentrations studied in adults. This is presumably a result of use-dependent drug binding leading to the frequency-dependent effects of verapamil on hERG current. We hypothesize that the elevated ranolazine levels may have had proarrhythmic effects coupled with proarrhythmia from verapamil. On switching to diltiazem, peak concentrations are noted at 4 hours. However, episodes of torsades persisted even with adequate trough and very high peak ranolazine levels.

As a final desperate measure we added phenytoin, and there was complete cessation of torsades. Phenytoin has a half-life of 12–36 hours and is a commonly used anticonvulsant with class IB antiarrhythmic properties that has been used in patients with refractory ventricular arrhythmias. It has effects on Na⁺, Ca²⁺, and K⁺ channels in cardiac myocytes and Purkinje fiber cell membranes. Inhibition of rapid inward Na⁺ current shortens the action potential and reduction of voltage-dependent calcium current reduces the rate of depolarization in the plateau phase of the cardiac action potential and increases the refractory period, thus preventing EADs. The phenytoin trough level was maintained at the high therapeutic range (15–20 mcg/mL). The addition of phenytoin resulted in a marked decline in ranolazine levels, as phenytoin is a potent inducer of CYP3A. There were no further episodes of TdP on

**Figure 3** Electrocardiogram showing A-paced rhythm at a rate of 100 beats per minute with QTc of 595 msec.
phenytoin and mexiletine with a low dose of ranolazine, so after 5 months the ranolazine and diltiazem were discontinued, with no recurrence of torsades after 2 months of follow-up. In our patient the addition of phenytoin was the final drug needed to achieve rhythm control.

Conclusion
The use of ranolazine in infants proves difficult owing to its short half-life and drug interactions leading to significant proarrhythmic side effects. In our patient we were unable to show a sustained positive therapeutic effect with ranolazine. Its efficacy may be greatest in those with isolated SCN5A mutations affecting the late sodium current. Caution must be used in patients with multiple mutations or additional polymorphisms owing to its multichannel effect. However, the pharmacokinetics would require every-4-hour dosing. The addition of a CYP3A inhibitor, such as verapamil or diltiazem, can extend the half-life to allow for every-6-hour dosing. Alternative CYP3A inhibitors can be considered as well, such as omeprazole. Finally, phenytoin should be considered in cases of malignant infant LQT3.

Acknowledgments
We are indebted to Gilead Science for the serial analysis of ranolazine levels done. Thank you to Caitlin Aberle, PharmD, for assisting in compounding the ranolazine suspension.

References
1. Van den Berg M, van den Heuvel F, van Tintelen J, Volders P, van Gelder I. Successful treatment of a patient with symptomatic long QT syndrome type 3 using ranolazine combined with a beta-blocker. Int J Cardiol 2014;171:90–92.
2. Bankston J, Yue M, Chung W, Spyres R, Siiver E, Sampson K, Kass R. A novel and lethal de novo LQT-3 mutation in a newborn with distinct molecular pharmacology and therapeutic response. PLoS One 2007;2:e1258.
3. Pietila E, Fodstad H, Niskasaari E, Laitinen P, Swan H, Savolainen M, Kesaniemi Y, Kontula K, Huikiri H. Association between HERG K897T polymorphism and QT interval in middle-aged Finnish women. J Am Coll Cardiol 2002;40:511–514.
4. Crotti K, Lundquist A, Insolia R, Pedrazzini M, Ferrandi C, De Ferrari G, Vicentini A, Yang P, Roden D, George A, Schwartz P. KCNH2-K897T is a genetic modifier of latent congenital long-QT syndrome. Circulation 2005;112:1251–1258.
5. Moss AJ, Zareba W, Schwarz KQ, Rosero S, McNitt S, Robinson JL. Ranolazine shortens repolarization in patients with sustained inward sodium current due to type-3 long QT syndrome. J Cardiovasc Electrophysiol 2008;19:1289–1293.
6. Jerling M. Clinical pharmacokinetics of ranolazine. Clin Pharmacokinet 2006;45:469–491.
7. Zhang S, Zhou Z, Gong Q, Makielski JC, January TC. Mechanism of block and identification of the verapamil binding domain to HERG potassium channels. Circ Res 1999;84:989–998.
8. Yager N, Wang K, Keshwani N, Torosoff M. Phenytoin as an effective treatment for polymorphic ventricular tachycardia due to QT prolongation in a patient with multiple drug intolerances. BMJ Case Rep 2015; http://dx.doi.org/10.1136/ bcr-2015-209921.