Antiepileptic rufinamide and QTc interval shortening in a patient with long QT syndrome: case report

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Background
There is limited pharmacologic therapy to reduce the QT interval in hereditary long QT syndrome (LQTS).

Case summary
We describe a child with Allan–Herndon–Dudley syndrome, Lennox–Gastaut epileptic syndrome (LGS), and LQTS Type 1 (LQTS1). Rufinamide was added to his antiepileptic medications to improve seizure control and was noted to be associated with a marked improvement in electrocardiogram QT interval. To the best of our knowledge, this is the first reported case of successful pharmacologic shortening of the QT interval in LQTS1.

Discussion
This case report highlights the potential benefits of rufinamide, a drug associated with mild QT shortening in normal individuals, to markedly reduce and normalize QT duration in a subject with LQTS1.

Keywords
Case report • Long QT syndrome • Rufinamide

Learning points
• Medications that shorten the corrected long QT interval may be a useful adjunct therapy in hereditary long QT syndromes.
• Medications (including repurposed drugs) that shorten the corrected QT interval can be identified.
• Rufinamide, which produced mild shortening of QT interval in normal individuals, produced marked normalization of QT interval in a child with long QT 1 syndrome.

Introduction
Rufinamide (Banzel®, Inovelon®) is used as an adjunctive antiepileptic therapy for Lennox–Gastaut syndrome (LGS) in children and may also have efficacy for the treatment of partial seizures in adults. It is a novel triazole derivative and a benzazepinone class sodium channel blocker. It is thought to work by preventing sodium channels in the brain from switching from an inactive state to an active state. We present a case where rufinamide was used in a patient with Allan–Herndon–Dudley syndrome, LGS, and long QT syndrome (LQTS) that resulted in shortening of the QT interval.
Timeline
The timeline of electrocardiogram (ECG) QT changes in relation to rufinamide initiation and dosage.

Case presentation
A 7-year-old boy with Allan–Herndon–Dudley syndrome (a rare X-linked disorder of brain development caused by SLC16A2 gene mutations) and LGS (a progressive epilepsy syndrome that causes tonic and atypical absence seizures and intellectual disability) underwent treatment for intractable epilepsy. In keeping with this diagnoses, the patient has severe developmental delay and is wheelchair bound and non-verbal. At baseline, he has ~10–15 seizures per day of different types, lasting <30 s. Several of these seizures have been observed and recorded, with concomitant ECGs showing sinus rhythm only. His medications included Nadolol, Valproic acid, Clobazam, Prevacid, and Flovent.

The child’s ECG at age 4 years and 8 months revealed a rate-corrected QT interval (QTc = QT/RR^1/2) of 523 ms (Figure 1). Holter monitor at this time was essentially normal with low-average heart rate for age in keeping with his beta-blocker (Nadolol) therapy of 1.26 mg/kg/day. One month later, he had another ECG with a QTc of 493 ms. He was identified to have LQTS Type 1 (LQTS1) due to a KCNQ1 Leu273Phe mutation inherited from his mother. The mother’s mutation was identified using a clinical panel of long QT genes and demonstrated only this single mutation. The boy’s mutation was identified through a familial analysis assessing this single mutation only. The maternal grandfather is also known to have LQTS with QTc >500 ms.

This KCNQ1 mutation was originally reported in one of the original kindreds (K1777) identifying gene mutations underlying LQT1 syndrome,^1^ has been subsequently published in an additional seven long QT cohorts, is exceedingly rare in large ‘normal cohorts’ (ExAC, GnomAD) and has been functionally characterized as having typical features of long QT syndrome.2,3 It is reported as pathogenic in the ClinVar database and is a known gene mutation in the Human Gene Mutation Database. Thus, it meets the American College of Medical Genetics criteria as a pathogenic variant.

Figure 1 Electrocardiogram: QTc (before rufinamide) = 523 ms.
At age 5 years, the patient was started on a new antiepileptic, rufinamide, to improve seizure control. He was initially started on rufinamide 90 mg bid and after the fifth dose the ECG revealed a QTc of 455 ms. He was continued on rufinamide and it was titrated up to 180 mg bid x 3 days, then 280 mg bid x 3 days, then 320 mg bid x 3 days, and then continued on 400 mg bid (see timeline for dosages and corresponding measured corrected QT intervals). Corrected QT intervals were measured using a standard published technique, including during sinus arrhythmia. An ECG at 5 years and 9 months of age was normal, with a QTc at 430 ms. Holter was normal and repeat ECG was also normal with a QTc of 400 ms (Figure 2). The patient did not suffer from any side effects from rufinamide, and remains on therapy.

Discussion

Hereditary LQTSs cause prolongation of the QT/QTc interval and predispose to arrhythmias (particularly torsade de pointes) resulting in syncope, cardiac arrest, or sudden cardiac death.4,5 Currently, the mainstay of therapy is beta-blocker, with implantable cardioverter-defibrillator (ICD) and left cervical sympathectomy reserved for high-risk patients. The risk of torsade de pointes increases significantly with longer QTc interval, particularly when it is more than 500 ms. Pharmacotherapies that shorten the QTc interval are limited6,7, although Mexiletine added to beta-blocker therapy may help shorten the QTc interval in LQT3 patients, and potassium supplements may be beneficial in LQT2 patients, particularly if there is hypokalaemia.8 ICDs have a substantial risk of harm (7% complications) in children and adults with LQTS.9,10

The dangers of drug-induced QT prolongation led to regulatory implications for new drug approval including thorough QT studies, and such pre-clinical evaluation has now identified drugs that may shorten QT interval. There are differing opinions as to whether QT interval shortening represents an important safety concern.11,12 New drugs identified to shorten the QT interval might be potentially useful in the therapy of LQTSs, although their mechanism of QT shortening and effect on the different forms of LQTS would require study.

Rufinamide is an antiepileptic medication that is distinct from other antiepileptic drugs, and approved since 2008 as an adjunctive seizure medicine in children 4 years and older and adults with the LGS. LGS is a severe epileptic encephalopathy characterized by delayed psychomotor development, behavioural disorders, and multiple types of generalized seizures.13 Clinical trials with rufinamide showed a concentration-dependent degree of QT interval shortening.14 Schimpf et al.14 demonstrated a mean reduction of the corrected QT interval was 20 ms in 19 patients with LGS. The maximum individual difference in the QTc interval in a single patient between baseline and rufinamide treatment was -54 ms. This effect, however, has not been studied in patients with LQTS.

This case highlights a reduction in the QTc interval after the initiation of a new antiepileptic drug, rufinamide, in a patient with LQTS.
To the best of our knowledge, this medication has not been studied in patients with LQTS, and the marked normalization of QT interval observed has not been described. Rufinamide could be a potential therapy for patients with high-risk LQTS such as those with QTc >500 ms, prior cardiac arrest, cardiac events despite therapy, the severe and malignant variants like Jervell and Lange-Nielsen syndrome or Timothy syndrome (LQT8). Such application might target those with excessive recurrent events despite maximal therapy.

The precise mechanism(s) by which rufinamide exerts its antiepileptic effect is unknown. The results of in vitro studies suggest that rufinamide may prolong the inactive state of plasma membrane sodium channels. From that proposed mechanism LQT3 patients may have more potential benefit.

Our patient is known to have LQT1. The shortening of QTc interval in our patient is >100 ms between baseline and rufinamide treatment. It is likely that multiple mechanisms led to QTc shortening. Rufinamide caused more QTc shortening in our LQTS patient than has been seen in non-LQTS individuals taking this medication. We recognize that although QT prolongation is a significant marker of risk for events in LQTS, shortening the QT interval with medication will not necessarily reduce this risk. Further animal studies and clinical observations may enlighten us regarding the scope of this drug for potential clinical use.

Supplementary material

Supplementary material is available at European Heart Journal - Case Reports online.

Slide sets: A fully edited slide set detailing this case and suitable for local presentation is available online as Supplementary data.

Consent: The author/s confirm that written consent for submission and publication of this case report including image(s) and associated text has been obtained from the patient in line with COPE guidance.

Conflict of interest: none declared.

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Lead author biography

Dr Robert M. Hamilton is a children’s cardiologist, heart rhythm specialist, and senior associate scientist at The Hospital for Sick Children and Research Institute, Toronto, Canada. He is a senior electrophysiologist, manages an inherited arrhythmia clinic, and has gained a unique perspective on the clinical impact of hereditary heart rhythm conditions on children and families. His research is focused on expanding the understanding of these inherited arrhythmia conditions and improving their diagnosis.