ORIGINAL ARTICLE

Risk of cardiac events in Long QT syndrome patients when taking antiseizure medications

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Many antiseizure medications (ASMs) affect ion channel function. We investigated whether ASMs alter the risk of cardiac events in patients with corrected QT (QT_c) prolongation. The study included people from the Rochester-based Long QT syndrome (LQTS) Registry with baseline QT_c prolongation and history of ASM therapy (n = 296). Using multivariate Anderson-Gill models, we assessed the risk of recurrent cardiac events associated with ASM therapy. We stratified by LQTS genotype and predominant mechanism of ASM action (Na^+ channel blocker and gamma-aminobutyric acid modifier.) There was an increased risk of cardiac events when participants with QT_c prolongation were taking vs off ASMs (HR 1.65, 95% confidence interval (CI) 1.36–2.00, $P < 0.001$). There was an increased risk of cardiac events when LQTS2 (HR 1.49, 95% CI 1.03–2.15, $P = 0.036$) but not LQTS1 participants were taking ASMs (interaction, $P = 0.016$). Na^+ channel blocker ASMs were associated with an increased risk of cardiac events in participants with QT_c prolongation, specifically LQTS2, but decreased risk in LQTS1. The increased risk when taking all ASMs and Na^+ channel blocker ASMs was attenuated by concurrent beta-adrenergic blocker therapy (interaction, $P < 0.001$). Gamma-aminobutyric acid modifier ASMs were associated with an increased risk of events in patients not concurrently treated with beta-adrenergic blockers. Female participants were at an increased risk of cardiac events while taking all ASMs and each class of ASMs. Despite no change in overall QT_c duration, pharmacogenomic analyses set the stage for future prospective clinical and mechanistic studies to validate that ASMs with predominantly Na^+ channel blocking actions are deleterious in LQTS2, but protective in LQTS1. (Translational Research 2017;■:1–12)

Abbreviations: ASM = antiseizure medication; GABA = gamma-aminobutyric acid; ECG = electrocardiogram; LQTS = Long QT syndrome; Na^+Ch = Na^+ channel; QT_c = corrected QT; SCD = sudden cardiac death; SUDEP = sudden unexpected death in epilepsy

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AT A GLANCE COMMENTARY

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Background

Long QT syndrome (LQTS) is due to mutations in ion channel genes expressed in the brain and heart. LQTS patients are at a high risk of arrhythmias and sudden death. As there is a high prevalence of seizures in LQTS, and antiseizure medications act on ion channels expressed in the brain and heart, it is important to assess the cardiac safety of ASMs in patients with LQTS.

Translational significance

Pharmacogenomic analyses indicate there are LQTS genotype and antiseizure medication class specific risks of cardiac events. These results establish the basis for future prospective clinical studies, and mechanistic cellular and animal studies.

INTRODUCTION

ASMs are associated with an increased risk of sudden cardiac death (SCD) and sudden unexpected death in epilepsy (SUDEP.)[1-3] Many antiseizure medications (ASMs) alter ion channel activity.[3] For example, phenytoin, carbamazepine, and lamotrigine are Na^+ channel blockers, while phenobarbital is a gamma-aminobutyric acid (GABA) enhancing drug.[4-6] Many ASMs have multiple effects, some of which are incompletely understood. Since there is overlap in subtypes of ion channels expressed in the heart and brain,[7] it is important to assess the cardiac safety of ASMs.

There is not a clear consensus whether ASMs are associated with changes in electrocardiogram (ECG) measures and risk of arrhythmias.[8-12] Cellular expression studies indicate that several ASMs block the rapid delayed rectifier K^+ current (I_{Kr}), which contributes to action potential repolarization in the heart.[13,14] Yet, in both healthy and epilepsy patient populations, these ASMs that block I_{Kr} are not associated with corrected QT (QT_c) prolongation on the cardiac ECG or increased risk of arrhythmias.[10,15-17] Although none of the ASMs examined in this study are on the Credible Meds list of drugs that increase the risk of torsades-de-pointes,[18] it remains unknown whether ASMs are safe in patients with underlying inherited or acquired alterations in cardiac electrical function.

Long QT syndrome (LQTS) mutations disturb the balance between depolarizing and repolarizing currents throughout the cardiac activation-recovery process, leading to QT_c prolongation and an increased risk of arrhythmias and SCD.[19] There is also a strong association between LQTS and seizures.[20-22] We recently showed that LQTS patients with seizures exhibit an increased risk for ventricular tachyarrhythmias.[20] As many LQTS patients take ASMs for seizures, and ASMs are used for pain control and as mood stabilizers, it is important to assess whether ASMs affect the risk of cardiac arrhythmias in these populations.

Using the Rochester-based LQTS Patient Registry, we compared the rate and risk of recurrent cardiac events when participants with QT_c prolongation and a history of ASM therapy were taking (on) vs off ASMs. Since the registry includes a relatively large number of LQTS1 ($n = 46$) and LQTS2 ($n = 76$) participants on ASMs, we specifically assessed whether there were LQTS genotype differences in the risk of cardiac events when on ASMs. Owing to differing mechanisms of ASM action, we also assessed the risk of cardiac events when LQTS participants were on each or a combination of classes of ASMs (i.e., Na^+ channel blocker, GABA modifier, and concurrent Na^+ channel blocker and GABA modifier ASMs). We hypothesized ASMs are associated with an increased risk of cardiac events in patients with reduced repolarization reserve (i.e., those with QT_c prolongation).

METHODS

Study cohort. The Rochester-based LQTS Registry provides a wealth of clinical, pharmacologic, and genetic information about LQTS probands and their affected and unaffected family members.[19] LQTS diagnosis was made by QT_c prolongation and/or LQTS genetic testing. Information was collected from extensive baseline/enrollment and yearly follow-up participant questionnaires, genetic reports, and physician reports. Information important to this study included results from genetic testing, the dates of ECG measurements and cardiac events, as well as the name and start (on) and end (off) date of taking each medication. Patient reported information was confirmed by reviewing the initial and yearly physician reports. The period on ASMs and beta-adrenergic blockers was defined as the dates the participant reported in the enrollment and yearly follow-up questionnaires being prescribed the medication, plus the dates the medication was listed in the medical records.

The study included consented participants with QT_c prolongation and a history of ASM therapy, and stratified by LQTS genotype (LQTS1 vs LQTS2). Importantly, in every participant, there was a period where the participant was taking (on) an ASM, as well as off all ASMs. Therefore, we performed detailed