Ranolazine Safely Decreases Ventricular and Atrial Fibrillation in Timothy Syndrome (LQT8)

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Long QT eight (LQT8), otherwise known as Timothy syndrome (TS), is a genetic disorder causing hyperactivation of the L-type calcium channel Cav 1.2. This calcium load and the resultant increase in the QT interval provide the substrate for ventricular arrhythmias. We previously presented a case in a patient with TS who had a profound decrease in his burden of ventricular arrhythmias after institution of an L-type calcium channel blocker. Although this patient's arrhythmia burden had decreased, he displayed an increasing burden of atrial fibrillation and still had bouts of ventricular fibrillation requiring defibrillator therapy. Basic research has recently shown that ranolazine, a multipotent ion-channel blocker, may be of benefit in patients with LQT8 syndrome. This case report details the decrease of atrial fibrillation and ventricular fibrillation events in our LQT8 patient with the addition of ranolazine. (PACE 2012; 35:e62–e64)

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Timothy syndrome (TS), characterized as the eighth long QT syndrome (LQT8), is a genetic disorder noted as a *de novo* mutation of G406R on exon 8A causing hyperactivation (reduced inactivation) of the L-type calcium channel Cav 1.2.[1,3,4] Although TS is classically associated with syndactyly, TS 2 is the variant form that has been described in two patients without the webbed phenotype.[2] TS 1 and 2 patients display a prolonged QT interval and the propensity for severe ventricular arrhythmias. LQT8 patients have abnormalities with calcium loading, are more prone to torsades de pointes (TdP) displaying early after depolarizations, delayed after depolarizations (DADs), and increased transmural dispersion of repolarization (TDR).[4]

Previously we reported that verapamil, an L-type calcium channel antagonist, reduced the burden of ventricular arrhythmias in a TS 2 patient who was genotyped with a Cav 1.2 mutation.[3] The ventricular arrhythmias and internal cardioverter defibrillator (ICD) shocks decreased significantly when precalcium and postcalcium channel blocker ICD logs were reviewed. However, we continued to still note that our patient required occasional ICD therapy for ventricular fibrillation. Also, his burden of symptomatic (palpitations) atrial fibrillation events increased.[3] The patient's clinical improvement on verapamil was made possible by understanding the genetic channelopathy.

Recent data have suggested that ranolazine, a multipotent ion-channel blocker first studied as an antianginal, may be of benefit in patients with LQT8 syndrome despite its black box contraindication in LQT patients.[4] Ranolazine has been shown to inhibit IKr, late INa, late ICa, peak ICa, and INa-Ca and decrease TDR.[5,6] There has been concern that with its inhibition of IKr, QT prolongation and proarrhythmia would be a risk, especially in congenital LQT patients. Other reports have communicated that ranolazine has safely and effectively decreased the burden of atrial fibrillation, mainly through a mechanism of potent use dependent block of peak INa.[7] We tested the addition of ranolazine in a TS 2 patient to control his ventricular fibrillation and decrease his burden of atrial fibrillation.

Case Report

The patient is a 26-year-old man with TS 2, a variant of LQT8, who presents with sporadic ventricular tachyarrhythmias and recurrent persistent atrial fibrillation. The patient's genotype and clinical phenotype has previously been reported to respond favorably to verapamil in the treatment of his ventricular tachyarrhythmias.[3] His atrial fibrillation had been responding to periodic cardioversion and maintenance therapy with verapamil SR 240 mg daily and long-acting metoprolol 150 mg daily. Vaughn-Williams class I and III antiarrhythmic medications were avoided due to the severe prolongation of the patient's QTc and history of severe, frequent episodes of

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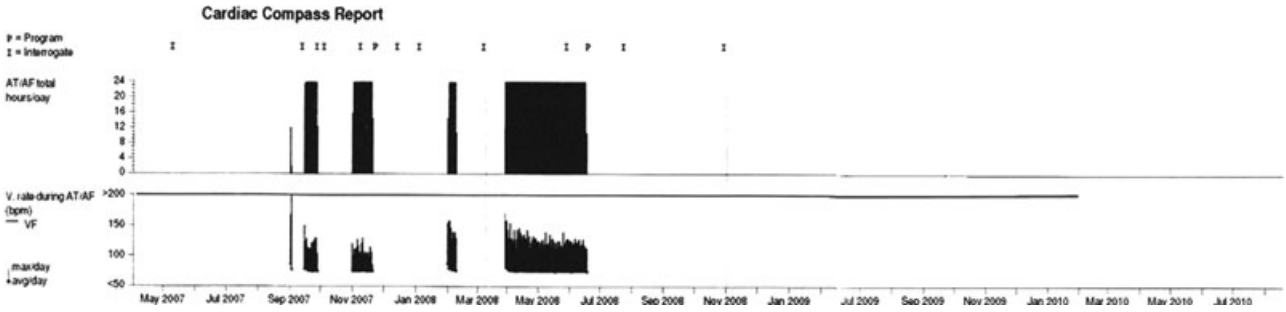

Figure 1. *Atrial fibrillation burden after the institution of ranolazine in September 2007. The burden of atrial fibrillation gradually decreased and only one brief episode has been recorded by the device in the past year and a half. AT/AF = atrial tachycardia/atrial fibrillation.*

ventricular fibrillation. The atrial fibrillation events, despite verapamil, became more persistent and his mental dysfunction worsened in association with the loss of atrial contraction.

A clinical decision was made to add ranolazine 500 mg twice a day, while maintaining the verapamil SR at 240 mg daily and discontinuing the β-blocker (Toprol XL 75 mg daily). His previous and continuing response to verapamil influenced us to continue its use. The pharmacologic transition to ranolazine was performed with in-patient telemetry monitoring for the first five doses. Monitoring of his JTc (100% paced to avoid oversensing T waves) was performed and demonstrated no increase after institution of ranolazine with a pre- and postranolazine JT/JTc interval of 420/466 ms and 390/436 ms, respectively. The patient tolerated the initiation of ranolazine without proarrhythmia or side effects acutely or chronically. We again compared the patient's ICD cardiac compass for arrhythmic burden pre- and postranolazine therapy (Fig. 1).

Table I indicates the chronic benefit of ranolazine in preventing ventricular tachyarrhythmias (VT/VF) in a patient with enhanced Cav 1.2 function who is also taking verapamil. The patient has been completely VT/VF free since ranolazine was added to verapamil. Figure 1 details the atrial fibrillation burden pre- and postranolazine and reveals a more gradual improvement in his atrial fibrillation burden, suggesting improved substrate remodeling may be present with the continued use of ranolazine.

Table I.

Ventricular Arrhythmia Burden and ICD Shocks

	Ventricular Arrhythmias	ICD Shocks
After verapamil 9/04–9/07	3 NSVT/1 VT/7 VF	8
After verapamil and ranolazine 9/07–2/10	0 NSVT/0 VT/0 VF	0

NSVR = nonsustained ventricular tachycardia; VT = ventricular tachycardia; VF = ventricular fibrillation.

Discussion

This is the first human case to report ranolazine's safety and efficacy in the treatment of arrhythmias in a LQT syndrome patient, specifically LQT8. In this case, the calcium channel-enhanced LQT8 patient responded favorably by decreasing his ventricular and atrial tachyarrhythmias without side effects or interactions with verapamil. Ranolazine by its multichannel inhibition can prolong refractoriness and increase the QT interval without increasing—and sometimes decreasing—TDR similar to amiodarone.[5,6,8] Ranolazine's QT prolonging properties led to labeling a black box warning against its use in long QT syndromes. In a large study of patients with acute coronary syndrome, ranolazine was not found to be proarrhythmic and significantly reduced the burden of ventricular tachycardia and supraventricular tachycardia including atrial fibrillation.[8,9] Animal models and small case series have shown its benefit in atrial fibrillation and reducing pulmonary vein triggers.[10–12] The increased atrial selectivity of ranolazine likely accomplishes this by its use dependence block of the peak sodium channel by prolonging the atrial effective refractory period and conduction time.[7,10,11]

Genotype and phenotype heterogeneity of LQT syndromes is common and affects young patients. LQT8 has been an extremely rare LQT subtype with very limited adult age patients due to the aggressive nature of ventricular arrhythmias leading to early infant death. Our patient has a random variant of exon 8a that rendered the

patient unable to control L-type calcium channels throughout his body but significantly in the heart. Although L-type calcium blockade was useful in our adult patient, it is generally not recommended in pediatric populations due to developmental retardation, both mental and musculoskeletal. Ranolazine's multipotent affect may be an answer in pediatric patients but needs to be further evaluated for developmental retardation.

When applied to the specter of LQT, ranolazine has decreased the ventricular arrhythmia burden in LQT2 and LQT3 in experimental models.[5] A recent publication using a left ventricular wedge model of TS revealed a reduction in triggered activity, VT, TdP, and DADs with ranolazine.[4,5] Assembly of a large clinical trial evaluating the safety and efficacy of ranolazine in LQT patients is not feasible. Despite no human data existing on ranolazine and LQT8, we were prompted to add or change this patient's antiarrhythmic drug therapy due to his uncontrolled atrial fibrillation burden and worsening mental capacity. Previous bench experiments, which indicated TS as the ideal LQT syndrome likely to respond to ranolazine's multipotent cardiac ion-channel blockade, allowed us to consider the use of ranolazine in our patient.[4–6,8] The ability of ranolazine's selectivity as a potent late INa channel blocker in the ventricle and a potent use dependent blocker of peak INa in the atrium likely contributed to its success in decreasing both ventricular and atrial arrhythmias.[7] This ability to bridge between basic science and clinical practice helped us manage the arrhythmic burden with pharma and care for a complex LQT patient.

Conclusions

Ranolazine appears effective and safe in the treatment of ventricular and atrial tachyarrhythmia in TS and its variants (LQT8).

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