CASE REPORT

A case report: Is mexiletine usage effective in the shortening of QTC interval and improving the T-wave alternans in Timothy syndrome?

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Timothy syndrome (TS) is a multisystemic disease that occurs because of a mutation in *CACN1C* gene and is characterized by prolonged QT interval. Mexiletine is a Class 1B antiarrhythmic drug that causes the disappearance of T-wave alternans by shortening QTc and peak-to-end of the T wave. It may block the development of torsades de pointes in a prolonged QT. This study presented the case of a patient diagnosed with TS and had a cardiac arrest history, prolonged QT, and T-wave alternans. After mexiletine treatment, the QTc interval shortened and T-wave alternans disappeared. Such a case has rarely been seen in the literature, and hence considered rare. This case presentation was of particular importance because it highlighted the use of mexiletine besides an initial beta-blocker treatment in the cases with TS.

KEYWORDS

cardiac arrhythmia, child, mexiletine, Timothy syndrome

1 | INTRODUCTION

Timothy syndrome (TS) is a rare multisystemic disease characterized by facial deformation, malignant ventricular arrhythmia, syndactyly, immune deficiency, intermittent hypoglycemia, autism, retardation of neurocognitive development, and prolonged QT interval. It occurs because of an activating mutation in *CACNA1C* gene, which codes L-type calcium channels (Splawski et al., 2004).

Mexiletine is an antiarrhythmic drug belonging to Class 1B group. It blocks late sodium channels. Mexiletine shortens QTc and peak-to-end of the T-wave (Tpe) intervals and causes the disappearance of T-wave alternans. Moreover, the Tpe/QT ratio decreases, and bradycardia causes QT and Tpe prolongation. It may block torsades de pointes arrhythmia via the aforementioned effects in the cases who have prolonged QT syndrome (Badri et al., 2015).

A child with TS was presented with a cardiac history, syndactyly, prolonged QT, and T-wave alternans. Her *CACNA1C* mutation test was positive, and an implantable cardioverter defibrillator (ICD) was installed. Since this was the second case whose QTc shortened and T-wave alternans was retarded after mexiletine administration, it was worth presenting.

2 | CASE REPORT

A 4-year, 6-month-old female patient was hospitalized in the intensive care unit at another health care center after a resuscitation application because of cardiac arrest. The case, who had several torsades de pointes and ventricular fibrillation attacks in the intensive care unit, was directed to our hospital due to the detection of prolonged QTc in her electrocardiography (ECG). As the patient's neuromotor development was found to be normal in the preliminary examination, her physical examination showed that she had whole-body hypertonicity and contracture in her feet secondary to hypoxia. She had syndactyly between her second and third toes of each foot. Her other systemic examinations were normal. The ECG at arrival showed a normal sinus rhythm, with a heart rate of 117 per min and QTc value of 606 ms (Figure 1). The basal rhythm was a normal sinus rhythm in her Holter ECG records, her QTc interval was extremely long (>600 ms), and she had a T-wave alternans. Her echocardiographic examination showed no pathology except foramen ovale. Since the patient had syndactyly and prolonged QTc, it was thought that she might have TS. A positive Pg406R mutation was detected in her *CACNA1C* gene. As a secondary prevention, an epicardial ICD was installed in the patient,

FIGURE 1 Baseline ECG showing QT prolongation and T-wave alternans

and propranolol treatment (6 mg/kg per day) was started. However, neither an adequate reduction in the heart rate nor any improvement in the T-wave alternans could be achieved with the propranolol treatment. An additional mexiletine treatment was started with 5 mg/kg per day and increased to 15 mg/kg per day. In her consecutive ECG measurements, her heart rate was 110 per min, QTc value decreased to 480 ms, and T-wave alternans disappeared (Figure 2). She was discharged from the hospital because ventricular arrhythmia and ICD shock were not observed in her follow-ups. Neither T-wave alternans nor ventricular arrhythmia was observed in her ECG and ICD records during the 11-month outpatient follow-ups.

3 | DISCUSSION

TS, which is also known as long QT type 8, is a rare case, and the number of such cases is <35 (Gao et al., 2013). In Turkey, the first case with TS was reported by Ergul, Ozyilmaz, Haydin, Guzeltas, & Tuzcu (2015). Depending on extremely prolonged QT, cases are usually lost because of ventricular fibrillation and torsades de pointes when they are around 2.5 years old. Some intrusive infections, severe diseases, and anesthesia applications may trigger malignant arrhythmia (Splawski et al., 2004, 2005). Only a few cases can overcome childhood (Napolitano, Splawski, Timothy, Bloise, & Priori, 1993). The present case was diagnosed with cardiac arrest when she was 4.5 years old. In TS, the inner calcium flow occurs during the plateau phase of the action potential depending on the L-type calcium channel activation. This situation delays repolarization and causes T-wave alternans. Any changes in the shape, amplitude, frequency, or polarity of the sinus rhythm of the T wave in EKG, without having any clear difference in QRS, are called T-wave alternans. This situation correlates with the extent of repolarization delay in patients with a prolonged QT and may cause malignant ventricular arrhythmia, which is a precursor of torsades de pointes (Zareba, Moss, le Cessie, & Hall, 1994).

The ICD is the most effective protection from sudden cardiac arrest due to prolonged QT syndrome-related ventricular arrhythmia.

FIGURE 2 Electrocardiogram after mexiletine treatment showing disappearance of T-wave alternans

Moreover, some antiarrhythmic drugs such as beta-blockers, mexiletine, calcium channel blockers, and ranolazine are used to block ventricular arrhythmias (Gao et al., 2013; Jacobs, Knight, McDonald, & Burke, 2006; Krause, Gravenhorst, Kriebel, Ruschewski, & Paul, 2011; Sicouri et al., 2007).

Mexiletine is a Class 1B antiarrhythmic drug that blocks late sodium channels (INA-L) without inducing calcium channel blockage (Gao et al., 2013). In the mexiletine-dependent INA-L blockage, repolarization shortens and repolarization dispersion decreases, early after depolarizations are suppressed, and torsades de pointes is blocked (Shimizu & Antzelevitch, 1997, 1998). Although the incidence of reported side effects with mexiletine ranges from 28 to 63%, the incidence of serious side effects necessitating a reduction in dose or discontinuation of the drug is low to modest. The predominant neurologic side effect is dizziness and lightheadedness occurring in up to 25% of patients. Tremor, nervousness, and ataxia occur in approximately 10% of patients. The gastrointestinal side effects include nausea, anorexia, and gastric

irritation and occur in up to 40% of patients. Overall, the frequency of side effects which require discontinuation of the drug or reduction in dosage is low (Manolis, Deering, Cameron, & Estes, 1990).

Gao et al. (2013) compared the effects of diltiazem, propranolol, and mexiletine used for treating TS. A significant bradycardia, a prolonged QT interval, and an evident T-wave alternans were observed when diltiazem and propranolol were administered together. However, a declined T-wave alternans and a shortened QT interval without bradycardia development were observed. Her QT interval did not shorten and no regression was observed in her T-wave alternans when propranolol was administered, as shown by Gao et al. (2013). When mexiletine was added to propranolol, QT interval significantly shortened and T-wave alternans was regressed. No ventricular arrhythmia attacks were observed during the 11-month follow-ups.

Consequently, a possibility of TS should be considered in patients who have prolonged QT, T-wave alternans, syndactyly, and dysmorphic face appearance. Mexiletine should be kept in mind to avoid T-wave alternans, which is considered as a precursor of fatal torsades de pointes arrhythmia depending on the development of a delayed repolarization or in the cases in which QTc interval needs to be shortened. Moreover, further studies should be conducted on the use of mexiletine besides beta-blockers in a higher number of cases for the initial treatment of TS.

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None.

CONFLICTS OF INTEREST

None.

ETHICAL STANDARDS

The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national guidelines on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008, and has been approved by the institutional committees.

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