GENETIC CORNER

Effect of Flecainide on T-Wave Alternans in Andersen–Tawil Syndrome

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INTRODUCTION

Andersen–Tawil syndrome is a heterogeneous disorder characterized by periodic paralysis, ventricular arrhythmias, QT prolongation, craniofacial dysmorphic features, and autosomal dominant inheritance. Most patients have a mutation in the ion channel gene, *KCNJ2*, which encodes the inward rectifier K⁺ channel Kir2.1, a component of the inward rectifier I_{K1}. T-wave alternans, defined as a beat-to-beat change in the amplitude and/or shape on the electrocardiogram (ECG), has been reported as a presage of life-threatening events. Nowadays, measurement of microvolt-level T-wave alternans that reflects a quantifiable, fundamental electrophysiologic property linked to life-threatening ventricular arrhythmias is a feasible procedure in clinical practice. However, it is not known that T-wave alternans is associated with ventricular arrhythmia in Andersen–Tawil syndrome. It was reported that flecainide was effective in suppressing ventricular tachyarrhythmia in Andersen–Tawil syndrome.^{1–3} Therefore, we evaluated the effects of flecainide on T-wave alternans and ventricular arrhythmia in this syndrome.

CASE PRESENTATION

Here we report a case of Andersen–Tawil syndrome whose exercise-induced T-wave alternans was almost suppressed by oral administration of flecainide. A 22-year-old human was introduced to the cardiology clinic of our university hospital because of change of residence. He was diagnosed as Andersen–Tawil syndrome at the age of 18 years. His height was 63.8 inches; his weight, 117 pounds. Physical examination on the chest was unremarkable. He has a family history of Andersen–Tawil syndrome in his younger sister who suffered from periodic paralysis and had QT prolongation. This patient did not have any symptoms relating to Andersen–Tawil syndrome. The gene analysis of this case revealed a mutation (c.200G > A p.R67Q) in *KCNJ2*.

He had been treated with atenolol (50 mg/day) and mexiletine (200 mg/day). To test the effects of flecainide, mexiletine was taken off. One month after the discontinuation of administration of mexiletine, 12-lead ECG recording, treadmill exercise test, and 24-hour ambulatory ECG recording were performed with use of atenolol (50 mg/day) alone. A 12-lead ECG showed a sinus rhythm

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Figure 1. Recordings taken under the administration of atenolol (50 mg/day) alone. (A) Resting 12-lead ECG recording. (B) Frequency of PVCs and HR during treadmill exercise testing. Asterisk points the time when T-wave alternans was measured. (C) T-wave alternans in lead V₅ during exercise. The number indicates the magnitude of T-wave alternans. Vertical bar indicates 1 mV.

and prolonged QT interval (Fig. 1A). Frequent premature ventricular contractions (PVCs) were present. Although most PVCs arose during the period of U wave with the coupling interval of 520 ms, one PVC (asterisk) emerged from the baseline level. Treadmill exercise test was carried out according to a standard Bruce protocol. The number of PVCs progressively increased, as heart rate (HR) increased from 2 minutes after the exercise began (Fig. 1B). However, the alteration of the number of PVCs did not parallel correspond to the increase in HR: that is, it gradually decreased after the exercise continued for 10 minutes and finally PVC rarely occurred from 12 minutes after the exercise initiation. The quantification of microvolt T-wave alternans was obtained when the PVCs diminished during the exercise testing. T-wave alternans was assessed based on the time-domain modified moving average analysis using commercially available software (GE Healthcare

Medical Systems, Milwaukee, WI, USA). The amplitude of T-wave alternans was 243 μ V in lead V₅, when HR was 160 beats/min (Fig. 1C). Twenty-four-hour ambulatory ECG recording revealed that PVCs were frequently present: the total number of PVCs, 19,389/day; couplet PVCs, 2964/day; triplet PVCs, 91/day; and nonsustained ventricular tachycardia, 4 times/day. After these tests were completed, flecainide (100 mg/day) was administered in addition to atenolol (50 mg/day).

One month after atenolol and flecainide were administered, 12-lead ECG recording, treadmill exercise test, and 24-hour ambulatory ECG recording were repeated. Twelve-lead ECG showed a sinus rhythm of 48 beats/min and no PVC (Fig. 2A). QT interval shortened to 440 ms, and corrected QT interval by Bazett's formula was 391 ms. During treadmill exercise testing, PVCs rarely occurred (Fig. 2B), although the HR response to exercise was identical to that of the previous

Figure 2. Recordings taken after the administration of flecainide (100 mg/day) in addition to atenolol (50 mg/day). (A) Resting 12-lead ECG recording. (B) Frequency of PVCs and HR during treadmill exercise testing. Asterisk points the time when T-wave alternans was measured. (C) T-wave alternans in lead V₅ during exercise. The number indicates the magnitude of T-wave alternans. Vertical bar indicates 1 mV.

treadmill exercise test. T-wave alternans was almost diminished during treadmill exercise test (23 μ V in lead II; Fig. 2C) even with the comparable HR to the previous treadmill test. Compared to the previous 24-hour ambulatory ECG recording, the total number of PVCs decreased: single PVC, 10,854/day; couplet PVCs, 245/day; triplet PVCs, 9/day; and quadrate PVCs, 1/day.

DISCUSSION

In this case, the administration of flecainide in addition to atenolol was effective to reduce T-wave alternans during exercise testing, concomitant with the shortening of QT interval and the substantial reduction of PVCs.

T-wave alternans reflects beat-to-beat fluctuation in T-wave shape and amplitude. T-wave alternans in microvolt levels was associated with increased risk of ventricular tachyarrhythmias

and occurrence of sudden cardiac death in a clinical setting.^{4,5} T-wave alternans represents temporal and/or spatial dispersion of ventricular repolarization. The relation between action potential duration and preceding diastolic interval, which is called restitution property, contributes to temporal alteration in action potential duration and conduction velocity. Spatial heterogeneity of repolarization may result in discordant alteration, which occasionally causes 2:1 conduction to occur, thus facilitating reentry. Another mechanism of T-wave alternans is that alternation of cytosolic calcium may underlie action potential duration alternans, because intracellular calcium cycling affects action potential duration.^{6,7} Intracellular Ca²⁺ cycling becomes alternating under physiologic or pathophysiological conditions, leading to T-wave alternans. In addition, excessive cytosolic calcium induces afterdepolarizations, which has potential to initiate ventricular tachyarrhythmias. In our case, the number of PVCs on treadmill exercise test

and Holter ECG recording decreased parallel with reduction of the magnitude of T-wave alternans.

The primary ion channel abnormality in Andersen-Tawil syndrome is a reduction of the inwardly rectifying potassium current, IK_1 channel. This causes prolongation in the terminal phase of the cardiac action potential triggering early after depolarizations. The depressed IK_1 function also leads to cellular calcium overload through sodium-calcium exchanger, causing late after depolarizations. It was reported that flecainide was effective to suppress ventricular arrhythmias in Andersen-Tawil syndrome.¹⁻³ The mechanism by which flecainide suppresses ventricular tachyarrhythmias in Andersen-Tawil syndrome is thought as follows: (1) reduction of cell excitability by decreased Na^+ current, (2) increase of Na^+ excretion via Na^+-Ca^{2+} exchanger, (3) decrease of sarcoplasmic reticulum calcium overload. Thereby, these effects may lead to suppression of T-wave alternans and triggered ventricular activity.

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