## Abstract

***Background:*** Andersen-Tawil syndrome (ATS) is an autosomal dominant genetic or sporadic disorder characterized by ventricular arrhythmias (VAs), periodic paralyses, and dysmorphic features. The optimal pharmacologic treatment for VAs in patients with ATS remains unknown.

***Objective:*** We evaluated the efficacy and safety of flecainide for VAs in patients with ATS with *KCNJ2* mutation.

***Methods:*** Ten ATS probands (7 female, 27±11 years old) were enrolled from 6 institutions. All of them had bidirectional VAs in spite of treatment with β-blockers (n=6) but none of them had either aborted cardiac arrest or family history of sudden cardiac death. Twenty-four-hour Holter recording and treadmill exercise testing (TMT) were performed before (baseline) and after oral flecainide treatment (150±46 mg/day).

***Results:*** Oral flecainide significantly reduced the total number of VAs (from 38407±19956 to 11196±14773 /day; p=0.003) and the number of the longest ventricular salvos (23±19 to 5±5; p=0.01) according to Holter recordings. At baseline, TMT induced non-sustained ventricular tachycardia (n=7) or couplets of premature ventricular complex (n=2); treatment with flecainide completely (n=7) or partially (n=2) suppressed these exercise-induced VAs (p=0.008). On the other hand, QRS, QT interval and U-wave amplitude of electrocardiogram were not altered by flecainide therapy. During a mean follow-up of 23±11months, no patients developed syncope or cardiac arrest after oral flecainide.

***Conclusion:*** This multi-center study suggests that oral flecainide therapy is an effective and safe means of suppressing VAs in patients with ATS with *KCNJ2* mutations, though the U-wave amplitude remained unchanged by flecainide.



**Key words**

Andersen-Tawil syndrome, long QT, flecainide, ventricular arrhythmia, mutation

**Abbreviations**

ATS: Andersen-Tawil syndrome

VA: ventricular arrhythmia

PVC: premature ventricular complex

TMT: treadmill exercise test

ECG: electrocardiogram

## Introduction

Andersen-Tawil syndrome (ATS) is a heterogeneous, autosomal dominant genetic or sporadic disorder characterized by ventricular arrhythmias (VAs), periodic paralyses, and dysmorphic features.[1, 2] ATS is a channelopathy linked to mutations in *KCNJ2* gene encoding the α-subunit of Kir2.1.[3-6] ATS patients often have a variety of VAs such as premature ventricular complexes (PVCs), polymorphic ventricular tachycardia (VT), and bidirectional VT. Although the cycle length of VAs in patients with ATS is relatively long and fatal cardiac event is rare, VAs often occur and lead to symptoms such as syncope and palpitations.[7] Moreover, sudden cardiac death and tachycardia-induced cardiomyopathy in ATS patients have been also reported. [8, 9] Thus, VA suppression is clinically important for ATS patients.

Although β-blockers and calcium channel blockers have been used to treat VAs in ATS,[7, 10-12] these drugs do not sufficiently suppress VAs. As an alternative, empirical case reports have suggested that flecainide might be effective at suppressing VAs in patients with ATS.[7, 8, 13] To date, however, there are few systematic evaluation of oral flecainide as a treatment for VAs in patients with ATS. Accordingly, this study aimed to assess the efficacy and safety of flecainide for VAs in ATS patients with *KCNJ2* mutations.

## Methods

### *Study Population*

The study population consisted of 10 unrelated ATS probands from 6 institutions in Japan who were treated with oral flecainide. We prospectively enrolled ATS patients who were expected to use flecainide as a treatment for VAs. Patients who could not perform treadmill exercise test (TMT), and more than 80 years old were excluded from this study. ATS was diagnosed based on clinical features such as VAs, episodes of periodic paralysis, and/or dysmorphic features as well as the presence of the *KCNJ2* genetic mutation. Cardiac involvement was determined based on the presence of VAs (PVC, polymorphic VT, and/or bidirectional VT), prolongation of the corrected QT

(U) interval (QTc or QUc) and/or enlargement of the U-wave on a 12-lead electrocardiogram (ECG).[1-6] The presence of periodic paralysis was diagnosed according to the standard criteria.[14] Dysmorphology was defined as the presence of two or more of the following: (a) low-set ears, (b) hypertelorism, (c) small mandible, (d) clinodactyly, and (e) syndactyly.[4]

To evaluate the efficacy of flecainide, 24-hour Holter recording and TMT were performed in all patients before (baseline) and after flecainide therapy. Dosage of flecainide was determined by the physician who treated the patient in this study. Physicians usually administered 2 to 3 mg/kg of flecainide and titrated according to the result of Holter recording, TMT, blood concentration of flecainide, and patient intention. All participants provided written informed consent according to the protocol approved by the institutional review board (M24-028-2).

***Twelve-lead ECG***

A 12-lead ECG was recorded at a paper speed of 25 mm/sec during sinus rhythm in the supine resting state in all patients. The R-R, PR, QT, QU, Tpeak-Upeak intervals, and QRS duration were measured. The QT interval was defined as the period from the onset of QRS to the end of the T-wave. The U-wave was defined as an early diastolic deflection after the end of the T-wave,[15] and an enlarged U-wave was defined according to the following criteria: (a) wave amplitude $\geq$ 0.2 mV or (b) amplitude larger than preceding T-wave. T-wave and U-wave durations were defined as the periods from the onset of the T-wave and U-wave to the end of the T-wave and U-wave, respectively.[15] The end of the T-wave and that of the U-wave were the points at which tangents drawn to the steepest downslopes of the T-wave and U-wave, respectively, crossed the isoelectric line. T-wave and U-wave amplitudes and durations were also measured. The QU interval was defined as the period from the onset of QRS to the end of the U-wave. The amplitude of T-wave or U-wave was measured at each highest amplitude lead, whereas the U/T-wave ratio was calculated at the highest amplitude U-wave lead. The QT and QU intervals were corrected by applying Bazett's formula (QTc and QUc, respectively).[6] Polymorphic VT was defined as a VT with an irregularly variable axis of the QRS. Bidirectional VT was defined as a VT with a beat-to-beat

alternation of the QRS axis.[16]

***Mutation Analysis***

The protocol for genetic analysis was approved by the Institutional Ethics Committee and performed under its guidelines (M24-031-4). All patients provided informed consent before the genetic analysis. Genomic DNA was isolated from whole blood using a DNA analyzer (QIAGEN GmbH, Hilden, Germany).[17] Genetic screening for *KCNJ2* was performed by the direct sequencing method (ABI 3730 DNA Analyzer, Life Technologies, Carlsbad, CA, USA). The cDNA sequence numbering was based upon the GenBank reference sequence NM_000891.2 for *KCNJ2*.

***Holter Recording***

A 24-hour Holter recording was performed in all patients before and after flecainide therapy. The following parameters were used to assess the clinical efficacy and safety of flecainide: (1) total number of VAs, (2) number of the longest ventricular salvos and cycle length during the VT, and (3) number of episodes of VT (≥3 successive VA).

***Treadmill Exercise Test***

TMT using a standard or modified Bruce protocol was performed before and after the introduction of flecainide therapy. The following parameters were used to assess the clinical efficacy of flecainide: (1) number of the longest ventricular salvos and cycle length of the VT, (2) maximum number of VAs during a 10-sec period, and (3) VA score (1~4), which is defined as the severity of the worst VA during exercise as previously described.[18] VA score was defined by the worst VA during exercise; 1 = no or isolated VA, 2 = bigeminal VA and/or frequent VA (≥ 10 per min), 3 = couplet, and 4 = VT (≥ 3 successive VA). The VA score of 1 was considered to indicate complete suppression of VAs. Less dramatic improvements in VA score were considered to indicate partial suppression.

***Follow-up***

All patients were followed-up at outpatient clinics every one to three months, and 12-lead ECG was performed. We investigated the incidence of arrhythmic events, defined as syncope, aborted cardiac arrest, or sudden cardiac death, and the side effects of flecainide through examination of medical history, physical findings, blood tests, 12-lead ECG, chest X-ray, and/or echocardiography.

### *Statistical Analysis*

Continuous variables are expressed as the mean ± SD or numbers and percentages, as appropriate. The student t-test was used to compare data with continuous variables. Categorical variables were compared by a chi-square test. A $p$ value of $< 0.05$ was considered statistically significant.

## Results

### *Patient Characteristics*

The study population consisted of 10 genotype-confirmed ATS probands who received oral flecainide from six Japanese institutes (**Table 1**). Seven patients were female. Their average age at the start of flecainide treatment was 27 ± 11 (9–47) years old. Our cohort includes five patients (#3~6, 8) with a family history of ATS, which genotypes and phenotypes were described in the **Supplemental Figure**. Eight patients (80%) showed dysmorphic features, and two (20%) had a history of periodic paralysis. Two patients (20%) had both dysmorphic features and periodic paralysis.

No structural heart disease was observed by echocardiogram in any patients. All patients had VAs documented by 12-lead ECG, Holter recording, and/or exercise testing. Bidirectional VT had been documented in all patients. Six patients were symptomatic, exhibiting syncope (n = 5), palpitations (n = 2), or dizziness (n = 2). There were no cases of aborted cardiac arrest or with family history of sudden cardiac death.

Nine patients were found to have missense mutations in four different residues (R67G/Q/W, R218Q/W, G300V and G301T), and one has an insertion (76insT) in the *KCNJ2* gene. All of these are located in the N- or C-terminus, and seven of these

mutations have been previously reported.[19]

***Medical Therapy***

Total seven patients had been treated with multiple drugs prior to flecainide. The drugs previously administered were β-blockers, namely, bisoprolol (n=2), atenolol (n=2), propranolol (n=1) and propranolol + metoprolol (n=1); sodium channel blockers, disopyramide (n=1), mexiletine (n=1) and pilsicainide (n=1); and the calcium channel blocker, verapamil (n=1). All of them failed to suppress VAs.

Flecainide was administrated at a dosage of 200 mg/day in three patients, at 150 mg/day in two, and at 100 mg/day in five (average 140 ± 46 mg/day). In four patients, β-blocker was continued after flecainide.

***Twelve-lead ECG***

Figure 1 shows representative 12-lead ECGs of a 24-year old patient (Case #4) at baseline (**Figure 1A, 1B**) and after flecainide therapy (**Figure 1C**). Although this patient had been treated with propranolol 60 mg/day and verapamil 240 mg/day, frequent VAs including bidirectional VT were still observed (**Figure 1B**). After administration of flecainide, total number of VAs was remarkably reduced from 10,767 to 36 /day, although the U-wave amplitude and its distribution in 12-lead ECG were unchanged.

Table 2 summarizes the changes in ECG parameters in all ATS patients. Flecainide therapy caused no significant difference in heart rate, PQ interval, QRS duration, QTc interval, QUc interval, T- and U-wave amplitudes and durations, frequency of enlarged U-wave or number of leads recording U-waves. The U/T-wave ratio was also unchanged after flecainide treatment.

***Holter Recording***

Twenty-four-hour Holter recordings demonstrated that flecainide therapy significantly and consistently reduced the total number of VAs (38,407 ± 19,956 to 11,196 ± 14,773 /day, p=0.03) (**Figure 2A**) and the number of the longest ventricular salvos (23 ± 19 to 5 ± 5 /day; p=0.01) (**Figure 2B**). Flecainide significantly reduced the

number of VT episodes (1,175± 1,163 to 60 ± 167; p= 0.008): in seven patients, the total number of VAs was reduced more than 70% from the number at baseline; in four of these, flecainide completely eliminated VT. Flecainide therapy did not alter the cycle length of VAs (458 ± 72 to 488 ± 58 ms; p=n.s.). Several Holter recordings or TMT after flecainide and/or concomitant medication (β-blockers, verapamil) were performed in 6 patients (#1~5, #8). As shown in **Supplemental Table**, total number of VAs per day and longest ventricular salvos per day of each time were consistently reduced after flecainide therapy.

***Treadmill Exercise Test***

Exercise capacity (peak workload) was not different at baseline and after flecainide therapy (12.5 ± 4.2 vs. 13.3 ± 4.1 METS, p=n.s). Peak heart rate during exercise was also unchanged at baseline and after flecainide (155 ± 19 bpm vs. 160 ± 23 bpm; p=n.s). **Figure 3** shows a representative 12-lead ECG of patient #4 during TMT before (baseline) (**Figure 3A**) and after flecainide (**Figure 3B**). In this case, flecainide therapy remarkably suppressed an exercise-induced bi-directional VT. In summary, the VA score during TMT was improved in 9 of 10 patients after flecainide therapy. In particular, seven patients' VA scores were improved by more than two levels (**Figure 4A**). Furthermore, the maximum number of VAs in any 10 seconds during TMT was also significantly reduced after flecainide therapy (**Figure 4B**). Several TMT after flecainide were also performed in 4 patients (#1~4), and VAs score and the maximum number of VAs during 10-sec were reduced consistently in three patients except for patient #3. **(Supplemental Table)** These findings strongly suggested that flecainide may suppress exercise-induced lethal VAs in patients with ATS.

***Follow-up***

During a mean follow-up of 23 ± 11 months after starting oral flecainide, no patients had arrhythmic events. No symptoms such as syncope or palpitation were observed in any patient. One patient experienced leg fatigue after the administration of flecainide at 200 mg/day; this symptom was improved after the dose was reduced to 150 mg/day. No other side effects were observed in any patient during follow-up.

## Discussion

### *Main Findings*

There were several findings in this study. First, flecainide therapy decreased the number of VAs and the maximum number of VA salvos, although it caused no significant changes in any ECG parameters. It was thus effective for the suppression of VAs in ATS patients with *KCNJ2* mutations. Second, flecainide therapy was safe in ATS patients over a moderate-term follow-up period. Therefore, flecainide may reduce the risk of sudden cardiac death in ATS patients.

### *Medication for VAs in ATS with KCNJ2 Mutation*

*KCNJ2* encodes the α-subunit of inward rectifier potassium channels (Kir2.1), which carry a critical component of the cardiac inward rectifying $K^+$ current ($I_{K1}$).[20, 21] The $I_{K1}$ regulates the terminal phase of repolarization and maintains the resting membrane potential in cardiomyocytes and skeletal muscle.[20, 22, 23] In this study, we observed eight different mutations (including three novel) in five residues of the *KCNJ2* gene. Although we did not perform a functional analysis, most of these (R67Q, R67W, R218Q, R218W, and G300V) have been reported as loss-of-function mutations resulting in dominant-negative suppression of Kir2.1 channel function,[3-6] which prolongs the action potential duration (APD) across the ventricular wall and destabilizes the resting membrane potential.[4, 24] APD prolongation also elicits an increase in calcium influx, leading to intracellular calcium overload. In addition, subsequent spontaneous $Ca^{2+}$ release may depolarize the membrane potential to the threshold of L-type calcium channel via transient inward currents carried by the $Na^+$-$Ca^{2+}$exchanger.[4, 25, 26] APD prolongation, the instability of the resting membrane potential, and calcium overload result in the onset of delayed afterdepolarization (DAD).[4, 24]

β-blockers and calcium channel blockers had been regarded as the principle drugs for VAs in patients with ATS [10, 11, 27]. Studies on successful therapy using β-blocker and/or calcium channel blocker in patients with ATS were, however, limited

to case reports and the efficacy of these drugs were controversial. Bokenkamp et al reported that β-blockers, the mainstay for other types of LQTS, are ineffective for VA in ATS [13]. Similarly, the efficacy of calcium channel blocker is uncertain, in addition, calcium channel blockers have risk of torsades de pointes and syncope in ATS patients [10, 11, 13]. In this study, although β-blockers and/or $Ca^{2+}$ channel blockers were administrated in six patients to prevent VAs, these drugs could not suppress VAs. Flecainide is a potent antiarrhythmic drug that can be used to suppress VAs in patients with ATS, [8, 13] although a systematic evaluation of its efficacy and safety during follow-up remained unclear. Delannoy et al. retrospectively investigated cardiac characteristics and prognosis in ATS patients, in which the prognosis in ATS patients was relatively good, and the combined therapy of flecainide with β-blocker was efficient to prevent severe arrhythmic events.[7] Recent case report suggested that combined use of verapamil and flecainide was effective for suppression of VAs in ATS patients. [28]

Here, we prospectively demonstrated the efficacy of flecainide in detail by using 24-hour Holter recording and TMT as well as its safety over middle-term follow-up in ATS patients. In patient #2, the combination therapy of flecainide and β-blockers may be more effective for suppression of VAs in ATS patients compared with flecainide or β-blocker treatment only (**Supplemental Table**). Although we showed that VAs were suppressed by flecainide treatment in ATS patients, the reduction of VAs might not be sufficient in some patients. One possible explanation was that the dose of flecainide might be smaller in these patients, because VAs were flecainide dose-dependently improved in 3 (patient #1, 4, 8) of 4 patients although flecainide was less effective in one patient (#3) even in the higher dose. (**Supplemental Table**).

***Mechanisms of Flecainide Therapy***

The mechanism underlying the suppression of VAs by flecainide in ATS patients is not fully understood. One possible explanation is that inhibition of the sodium channel may directly suppress a trigger of arrhythmia and/or indirectly inhibit the $Na^{+}$-$Ca^{2+}$exchanger, resulting in reduced likelihood of intracellular $Ca^{2+}$ overload and decreased DAD.[29] As an alternative explanation, Caballero et al. have reported that

flecainide increases Kir2.1 channels, which increase $I_{K1}$ currents as recorded in ventricular myocytes.[21] In this study, however, as flecainide did not normalize the QU interval or the U wave amplitude, the effect of flecainide on increasing $I_{K1}$ seems to be not directly involved in the suppression of VAs.

Another possible mechanism underlying the antiarrhythmic effect of flecainide is a direct effect on RyR2 receptors. Some *KCNJ2* mutation carriers lack the ATS phenotype but share the catecholaminergic polymorphic ventricular tachycardia (CPVT).[17, 19, 30] Although it's not clear whether exercise is a trigger of VAs in ATS patients [31], five of ten patients had experienced syncope during exercise in this study.

Similar exercise-induced bi-directional VT is often observed in both ATS and CPVT. Watanabe et al. recently reported that flecainide not only blocked cardiac sodium channels but also directly inhibited RyR2, thus preventing CPVT.[32] These findings suggest that flecainide may affect $Ca^{2+}$ leakage from RyR2, resulting in the suppression of VAs in ATS as well as the suppression of CPVT.

***Limitations***

First, this study have evaluated the efficacy of flecainide on suppression of VAs using 24-hour Holter recording and treadmill exercise testing, but whether or not this short-term elimination of VAs contributes to suppress the subsequent cardiac events in this syndrome is still unclear. In addition, ATS patients without flecainide treatment have not been included in this study, which might raise a bias for patient's selection. Therefore, further investigations are necessary to show the long-term efficacy of flecainide for cardiac events in ATS patients.

Second, our study population of *KCNJ2*-positive ATS patients was relatively small because of the rarity. Larger numbers of patients with *KCNJ2* mutations are needed to evaluate the efficacy and safety of flecainide therapy for VAs in ATS patients. There appear to be several 'hotspots' for pathogenic mutations, including, notably, the arginine amino acids at positions 67 and 218 in the N-terminus and C-terminus, respectively;[19] these were also included in this cohort study. Therefore, flecainide may be effective for the suppression of exercise-induced VAs in many ATS patients with *KCNJ2* mutations.

Third, approximately 40% of patients with the phenotypic features of ATS do not have a *KCNJ2* mutation,[31, 33] suggesting the presence of other causative genes such as *KCNJ5*.[34] We did not assess the flecainide therapy in clinical ATS cases without *KCNJ2* mutation. Finally, there has previously been reported a family with ATS and dilated cardiomyopathy [35], but this study did not include such patients with LV dysfunction. Therefore, we could not assess efficacy and safety of flecainide in ATS with LV dysfunction.

## Conclusions

This multi-center study suggests that oral flecainide therapy is an effective and safe means of suppressing VAs in patients with ATS with *KCNJ2* mutations, though the U-wave amplitude remained unchanged by flecainide. Flecainide with or without conventional drug therapy should be considered for VA suppression in ATS patients.

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**Clinical Perspective**

Andersen-Tawil syndrome (ATS) is a heterogeneous, autosomal dominant genetic or sporadic disorder characterized by ventricular arrhythmias (VAs), periodic paralyses, and dysmorphic features. The VAs such as premature ventricular complexs, polymorphic ventricular tachycardia (VT) and bi-directional VT in ATS patients seems to be benign, but rarely lead to sudden cardiac death or tachy-induced cardiomyopathy. The β-blockers and calcium channel blockers have been used to treat VAs in ATS patients, however, their efficacy is limited. Recently, Na+ channel blocker, flecainide has been reported as an effective tool for suppression of the VAs in a patient with ATS. This multicenter study systematically evaluated the efficacy and safety of oral flecainide for ATS patients with *KCNJ2* mutations. The ECG parameters (QT, QU, U-wave amplitude, and U/T-wave ratio) were not significantly altered after flecainide, but parameters from the Holter recordings and treadmill exercise test can be useful as a marker for the efficacy of flecainide. Moreover, the exercise-induced bi-directional VT or polymorphic VT is observed not only in patients with ATS but also in catecholaminergic polymorphic ventricular tachycardia (CPVT). The clinical and electrocardiographic features including U-wave is sometimes similar between ATS and CPVT. Flecainide therapy has also been useful for suppression of VAs in CPVT, thus it should be available for the pre-diagnosed possible ATS or CPVT patients. Finally, flecainide therapy is safe in ATS patients without overt LV dysfunction although the patients in this study were not followed for a long-term period. Therefore, flecainide may reduce risk of sudden cardiac death in ATS patients.

# Figure Legends

**Figure 1.**

12-lead ECGs recorded from a 24-year old male proband (Case #4) with *KCNJ2* mutation before (**A**, **B**) and after flecainide therapy (**C**).

**A**: Before flecainide (propranolol 60 mg/day and verapamil 240 mg/day), PR interval (280 msec) indicated first-degree AV block, QTc was normal (< 440 ms), and U-wave was widely distributed in lead II, aVF, V1 to V5. Enlarged U-wave (wave amplitude ≥ 0.2 mV) was observed in V2 and V3, and QUc interval was 663 msec.

**B**: Bidirectional VT (cycle length 480 ms) in 12-lead ECG at baseline (asterisk). The QRS complexes showed alternating polarities, and a right bundle-branch block pattern was shown in the VT beats.

**C**: 12-lead ECG after administration of flecainide 200 mg in addition to propranolol 60 mg. Verapamil was discontinued after VA suppression by flecainide in this patient, and PR interval was reduced. Enlarged U-wave persists and remains widely distributed even after VA suppression by administration of flecainide.

ECG = electrocardiogram; VA = ventricular arrhythmia; VT = ventricular tachycardia.

**Figure 2.**

Total number of VAs and of the longest ventricular salvos per day from a 24-hour Holter recording before (baseline) and after flecainide therapy.

**A**. Total number of VAs per day was reduced after flecainide in all patients, most notably in seven patients whose VA counts were reduced by more than 70% from the baseline level.

**B**. The number of the longest ventricular salvos per day was also reduced after flecainide therapy in all patients.

Abbreviations as in Figure 1.

**Figure 3.** 12-lead ECG during TMT before (baseline) (A) and after flecainide therapy (B) in an ATS patient (case #4).

**A**: At baseline (propranolol 60 mg + verapamil 240 mg), frequent PVCs and nonsustained VTs (the longest ventricular salvo was 6 beats) (asterisk) were observed during exercise.

**B**: Flecainide 200 mg in addition to propranolol 60 mg suppressed exercise-induced VAs.

TMT = treadmill exercise test; other abbreviations as in Figure 1.

**Figure 4.** Effect of flecainide on exercise-induced VAs.

**A**. VAs during TMT are shown by VA score: 1 = no or isolated VAs, 2 = bigeminal VAs and/or frequent VAs (≥10 per min), 3 = couplets, and 4 =VT (≥3 successive VAs). VAs during TMT are compared before (baseline) and after flecainide in ATS probands with *KCNJ2* mutation. The line thickness indicates the number of patients. VA score was improved by flecainide therapy in 9 of 10 patients (90%). Flecainide therapy reduced VA score from 3.6 ± 0.7 to 1.6 ± 1.1 ($p = 0.008$).

**B**. The maximum number of VAs during any 10-sec interval during TMT at baseline and after flecainide therapy. Flecainide therapy reduced the maximum number of VAs during any 10-sec interval from 16±7 to 5±7 ($p = 0.002$).

Abbreviations as in Figures 1 and 3.

# Table 1
## Clinical, Mutational and Electrocardiographic Characteristics of all Probands with Andersen-Tawil Syndrome

| # | Mutation | Age /Sex | BW (kg) | Sympt | Sync | FH | Dysmorphism /Periodic paralysis | Bi-VT and/or poly-VT | Flecainide dose (mg/day, mg/kg) | Flecainide concentraion (ng/ml) | Medical treatment at baseline /concomitant with flecainide |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **1** | M301T | 27/F | 42 | + | - | - | +/- | + | 150, 3.6 | 278 | Bisoprolol / Bisoprolol |
| **2** | R67W | 41/F | 57 | + | + | - | +/- | + | 200, 3.5 | N/A | Bisoprolol, Disopyramide /Bisoprolol, Nicorandil |
| **3** | G300V | 29/F | 47 | + | + | + | +/- | + | 200, 4.3 | 507 | Atenolol / Atenolol |
| **4** | G300V | 24/M | 61 | + | + | + | +/- | + | 200, 3.3 | 324 | Propranolol, Verapamil /Propranolol |
| **5** | R218W | 13/M | 35 | - | - | + | +/+ | + | 100, 2.9 | N/A | Propranolol, Metoprolol /None |
| **6** | R67Q | 23/M | 53 | - | - | + | -/- | + | 100, 1.9 | N/A | Atenolol, Mexiletine /None |
| **7** | R218Q | 27/F | 46 | - | - | - | -/- | + | 100, 2.2 | 347 | None /None |
| **8** | R218W | 47/F | 46 | + | + | + | +/+ | + | 150, 3.3 | 532 | Pilsicainide /None |
| **9** | 76insT | 9/F | 26 | - | - | - | +/- | + | 100, 3.8 | N/A | None /None |
| **10** | R67G | 25/F | 45 | + | + | - | +/- | + | 100, 2.2 | N/A | None /None |

Synpt: symptom, Sync: syncope, BW: body weight, FH: family history, Bi-VT: bidirectional ventricular tachycardia, Poly-VT: polymorphic ventricular tachycardia

**Table 2**
**Electrocardiographic Changes after Flecainide Treatment in Patients with Andersen-Tawil Syndrome**

| | baseline | flecainide | p value |
|---|---|---|---|
| Heart rate, bpm | 68 ± 15 | 69 ± 17 | 0.97 |
| PQ interval, ms | 173 ± 41 | 178 ± 24 | 0.74 |
| QRS duration, ms | 93 ± 19 | 98 ± 18 | 0.55 |
| QTc interval, ms | 432 ± 26 | 448 ± 34 | 0.26 |
| QUc interval, ms | 667 ± 43 | 679 ± 35 | 0.50 |
| T-wave amplitude, mV | 0.55 ± 0.25 | 0.43 ± 0.20 | 0.24 |
| T-wave duration, ms | 290 ± 34 | 288 ± 43 | 0.91 |
| U-wave amplitude, mV | 0.21 ± 0.05 | 0.23 ± 0.05 | 0.49 |
| U-wave duration, ms | 215 ± 22 | 213 ± 25 | 0.85 |
| U/T-wave amplitude ratio at the highest amplitude U-wave lead | 0.50 ± 0.18 | 0.62 ± 0.20 | 0.17 |
| Enlarged U-wave, number of patients (%) | 8 (80) | 9 (90) | 0.53 |
| U-wave distribution, number of leads | 4.6 ± 1.9 | 4.7 ± 1.9 | 0.91 |

QTc interval: corrected QT interval by Bazett's formula