SHORT COMMUNICATION

Reduction of complex ventricular ectopy and improvement in exercise capacity with flecainide therapy in Andersen–Tawil syndrome

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Andersen–Tawil syndrome (ATS) is a rare inherited autosomal disorder characterized by the clinical triad of ventricular arrhythmias, hypokalaemic periodic paralyses, and skeletal developmental abnormalities, resulting in dysmorphic features. Although ATS patients have a high incidence of ventricular arrhythmias, the occurrence of sudden cardiac death is rare. In this report, we describe the successful use of flecainide in an ATS patient with a considerable ventricular arrhythmia burden who had not demonstrated any response to conventional β-blocker therapy used in conjunction with potassium (K⁺) supplementation.

Introduction

Andersen–Tawil syndrome (ATS) is a rare inherited autosomal disorder characterized by ventricular arrhythmias, hypokalaemic periodic paralyses, and skeletal developmental abnormalities producing dysmorphic features.² The majority of ATS cases are caused by mutations in the KCNJ2 gene, with over 20 different mutations having been described. This gene encodes the α-subunit of Kir2.1, an inward potassium rectifier channel responsible for cardiac myocyte repolarization. Andersen–Tawil syndrome has also been labelled as 'long QT syndrome 7'.

The electrocardiographic manifestations of ATS (particularly, in KCNJ2 mutation-positive cases) include QTc prolongation and prominent U-waves.² Ambulatory electrocardiography often reveals a large burden of premature ventricular complexes (PVCs), polymorphic ventricular tachycardia (VT), and bidirectional VT.

Although ATS patients have a high incidence of ventricular arrhythmias, the occurrence of sudden cardiac death is rare. Furthermore, a large ventricular arrhythmia burden over a long time period can be detrimental to the left ventricular function and lead to cardiomyopathy.

Given the potential negative impact of targeting ventricular ectopy in asymptomatic patients, the optimal therapy and therapeutic endpoints for ATS patients are unknown.

We describe the successful use of flecainide in an ATS patient with a considerable ventricular arrhythmia burden who had not demonstrated any response to conventional β-blocker therapy used in conjunction with potassium (K⁺) supplementation.

Case report

A 54-year-old man was diagnosed with ATS after several episodes of hypokalaemic paralysis. Direct sequencing demonstrated a G1132A point mutation in the KCNJ2 gene, resulting in a V302M amino acid change. He was of short stature (167 cm) and had a broad forehead with associated hypotelorism.

He was referred for cardiological assessment because of multiple PVCs and reduced exercise capacity. His baseline electrocardiogram showed right bundle branch block with prolongation of the QTc interval and prominent U-waves, typical of ATS (Figure 1).

Further investigations revealed a normal transthoracic echocardiogram. A 24 h Holter monitoring demonstrated frequent polymorphic PVCs, bidirectional VT, and non-sustained polymorphic VT (NSVT). The baseline 24 h monitor had 15 671
isolated PVCs, 1912 couplets, and 358 runs of NSVT. He had reduced exercise capacity limited by dyspnoea in conjunction with an increase in the frequency of all forms of ventricular arrhythmia. Baseline symptom-limited exercise tolerance testing (ETT) using a standard Bruce protocol produced a maximum exercise capacity of 3 min (6.3 METS). He was started on bisoprolol 5 mg daily in conjunction with oral K$^+$ supplementation. Repeat ambulatory monitoring demonstrated no significant reduction on his ventricular arrhythmia burden, with bidirectional VT and multiple PVCs still present on ambulatory monitoring (Figure 2), and no change in his functional exercise capacity.

He was therefore switched from bisoprolol to flecainide 100 mg bid. Holter monitoring and ETT, 2 weeks after the initiation of oral flecainide, showed a dramatic reduction in all forms of ventricular arrhythmias (PVCs, couplets, and NSVT), compared with both baseline and bisoprolol therapy. A 24 h period of ambulatory monitoring carried out on flecainide demonstrated only 268 PVCs, 11 couplets, and no runs of NSVT.

Repeat Bruce protocol ETT while on flecainide demonstrated a significant reduction in dyspnoea during exercise and a 38% increase in exercise capacity (peak workload rose from 6.3 to 8.7 METS).

**Discussion**

Andersen–Tawil syndrome is a rare genetic disorder with ∼100 cases reported in the literature. Ventricular arrhythmias are common and have been reported in over 80% of the ATS patients with characteristic bidirectional VT seen in approximately 30%. Currently, β-blockers are regarded as the principle cardiac medication to treat ventricular arrhythmias, along with the usual advice of avoidance of QT prolonging drugs, hypokalaemia, and adrenergic stimulation—such as aerobic exercise. However, β-blocker therapy is unproven and not always effective. Flecainide has recently been reported to be highly efficacious in suppressing ventricular arrhythmias in two siblings with ATS. Andersen–Tawil syndrome is heterogenous and demonstrates considerable phenotypic variability between patients and families. Flecainide has also recently been demonstrated to suppress bidirectional VT without any adverse effect.

The primary defect at the ion channel level is a reduction of the inwardly rectifying potassium current, $I_{K1}$, channel. This causes prolongation in the terminal phase of the cardiac action potential producing early afterdepolarizations. The depressed $I_{K1}$ function also leads to cellular calcium overload, causing late afterdepolarizations leading to triggered activity.

The mechanism by which flecainide suppresses ventricular arrhythmias is poorly understood. It is likely that the potent sodium channel blocking effect produced by flecainide interacts with the cell membrane sodium–calcium exchanger. This reduces sarcoplasmic reticulum calcium overload, thereby diminishing triggered ventricular activity.

Our ATS patient had a marked ventricular arrhythmia burden and reduced exercise tolerance, neither of which improved with β-blocker therapy. With the use of flecainide, he has shown a marked and persistent reduction in all forms of ventricular arrhythmia in conjunction with improved exercise capacity. Given these favourable observations, a future study of flecainide therapy for the treatment of ventricular arrhythmias in ATS is warranted.
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References

Figure 2: Ambulatory monitoring performed on our ATS patient demonstrating multiple PVCs and runs of non sustained bidirectional VT.