Case Report / Olgu Sunumu
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Propafenone Induced Takotsubo Cardiomyopathy: A Mere Coincidence or A New Causal Relationship?

Propafenona Bağlı Gelişen Takotsubo Kardiyomiyopatisi: Sadece Bir Tesadüf mü, Yeni Bir Nedensel İlişki mi?

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ABSTRACT

Propafenone is a class 1C antiarrhythmic drug that blocks sodium channels and is used in the treatment of arrhythmia. Because of its rapid effect on terminating paroxysmal episodes of atrial fibrillation, it can be used as a pill-in-the-pocket. In patients with structural heart disease, it is less preferred due to cardiotoxic effects in long-term use. Although propafenone use is known to cause several cardiovascular side effects, the development of Takotsubo cardiomyopathy is unknown. Propafenone toxicity at standard doses is a rare condition. Propafenone plasma concentrations may increase through inhibition of cytochrome P450 2D6 and complete inhibition of 2D6 metabolism can increase propafenone levels by up to 3 to 10 times. In this case report, we aimed to present a 37-year-old female patient who developed Takotsubo cardiomyopathy and cardiogenic shock after the first dose of propafenone use and recovered with medical treatment.
Keywords: Takotsubo; propafenone; cardiomyopathy.

ÖZ

Propafenon, sodyum kanallarını bloke eden ve aritmi tedavisinde kullanılan, sınıf 1C antiaritmik bir ilaçtır. Atriyal fibrilasyonun paroksismal ataklarını sonlandırmadaki hızlı etkisi nedeniyle "cep hapı" olarak kullanılmaktadır. Uzun süreli kullanımlarda meydana getirdiği kardiyotoksik etkilerinden dolayı yapısal kalp hastalığı olan bireylerde daha az tercih edilmektedir. Propafenon kullanımının çeşitli kardiyovasküler yan etkilere neden olduğu bilinmesine rağmen, Takotsubo kardiyomiyopatisi gelişimi bilinmemektedir. Standart dozlarda propafenon toksisitesi nadir olarak gözlenen bir durumdur. Propafenon plazma konsantrasyonları, sitokrom P450 2D6'nın inhibisyonu yoluyla artabilir ve 2D6 metabolizmasının tamamen inhibisyonu, propafenon düzeylerini 3 ila 10 kata kadar arttırabilir. Bu vaka sunumunda ilk doz propafenon kullanımı sonrasında Takotsubo kardiyomiyopatisi ve kardiyojenik şok gelişen ve medikal tedavi ile düzelen 37 yaşında kadın hastanın sunulması amaçlanmıştır.
Anahtar kelimeler: Takotsubo; propafenon; kardiyomiyopati.

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INTRODUCTION

Takotsubo cardiomyopathy (TC) is a reversible cardiomyopathy in which the left ventricular apical region is akinetic and basal parts are hyperkinetic. Although it may rarely have a mortal course, it usually resolves within a few weeks with supportive treatment (1). Although the pathophysiology is not known exactly, it has been reported that it may be secondary to high catecholamine release, rheumatological

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diseases such as systemic lupus erythematosus, and drug use (1-3). Although the development of TC secondary to anti-arrhythmic drugs such as flecainide has been reported, the development of TC due to propafenone use with the same mechanism of action is unknown (4,5). Development or exacerbating of TC secondary to propafenone use was first seen in our case.

CASE REPORT

A 37-year-old female patient was admitted to the emergency room with a presyncope. She had reported feeling unwell the evening of the presentation, with palpitation and chest pain. In the emergency service, she was found to be hypotensive with a systolic blood pressure of 50/30 mmHg and a heart rate of 73 beats/min. Other vital signs were normal (respiratory rate: 10/minute, SaO_2: 93% -without oxygen support-, and body temperature: 36.8 °C). Physical examination showed: pale color, cold extremities, low-amplitude pulses, and normal cardiac examination with no additional sounds and murmurs. There was also nothing remarkable in her lung examination.

In history, she had been seen by a cardiologist due to palpitation one year ago, and her cardiac examination was normal, but she had paroxysmal atrial fibrillation in a 24-hour Holter evaluation. She had been prescribed Propafenone 300 mg (Rytmonorm, Abbott) but she did not take the drug. Further questioning revealed that she had lost her child three years ago and had not had any other stress factors in recent days. Upon the onset of palpitation, she remembered the medicine prescribed by the doctor and took 4 tablets - 600 mg propafenone for the first time ever. Later, she was brought to the emergency service as her condition worsened and she was about to faint.

In the laboratory tests, her blood glucose level: 97 mg/dL, creatinine: 0.9 mg/dL, urea: 33 mg/dL, AST: 83 IU/L, ALT: 106 IU/L, sodium: 141 mEq/L, potassium: 3.9 mEq/L, magnesium: 1.9 mg/dL, calcium: 8.3 mg/dL, albumin: 3.4 g/dL, pH: 7.21, pO_2: 76 mmHg, pCO_2: 35 mmHg, HCO_3: 14 mEq/L, SaO_2: 92%, lactate: 4.2 mmol/L in arterial blood gas. Other biochemical tests were normal. D-dimer was 287 ng/mL (upper limit: 500 ng/mL) and troponin was 0.04 ng/mL (upper limit: 0.06 ng/mL). Her electrocardiography (ECG) showed slow atrial fibrillation and a wide QRS segment (180 ms) along with a long corrected QT interval (574 ms) (Figure 1A). Bedside transthoracic echocardiographic examination revealed akinetic left ventricular apex and hyperkinetic basal segments (Figure 2, Video 1). Cerebrovascular disease was excluded by cranial tomography and magnetic resonance imaging. The patient was hospitalized with a pre-diagnosis of cardiogenic shock and TC. Intravenous isotonic fluid with an infusion rate of 70 ml/h, dopamine with an infusion rate of minimal tolerated dosage -4 mcg/kg/min- to keep blood systolic pressure >100 mmHg and supportive sodium bicarbonate were administrated. The vital signs of the patient were followed up with continuous monitoring. Her ECG showed ST-segment elevation in D2, D3, and aVF with reciprocal ST-segment depression in D1 and AVL (Figure 1B) seen in control ECG upon she had stated chest pain. The patient was taken to the catheter laboratory with the diagnosis of acute inferior MI. Normal coronary arteries were observed in coronary angiogram while ventriculography revealed apical ballooning and hyperkinetic basal segments supporting the TC (Figure 3, Video 2). Later in her ECG follow-ups, V1 and V2 leads showed coved ST segment elevation that mimics channelopathy syndrome. An upper lead ECG was taken to confirm changes and the Brugada pattern became evident (Figure 1C). Following initial sodium bicarbonate administration with two ampules, continuous sodium bicarbonate infusion was started with one ampule/hour dosing. Within supportive treatment, her hypotension had resolved, and she was weaned off the dopamine and sodium bicarbonate infusions after 4 hours. The patient's hemodynamic values were maintained normal without any support. Blood gas parameters, QRS complex (78 ms), and corrected QT interval (473 ms) returned to normal on the day after hospitalization (Figure 1D). Liver function tests and

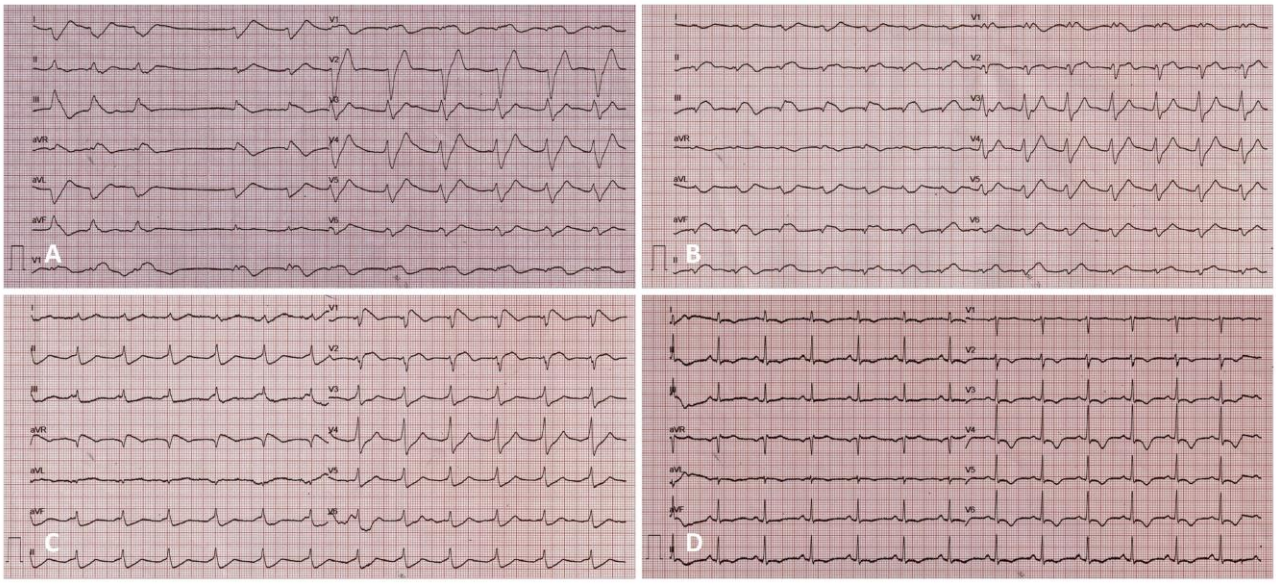


Figure 1. Electrocardiography; **A)** on arrival, **B)** ST-segment elevation in inferior leads, **C)** Brugada pattern, **D)** after treatment

echocardiographic parameters returned to normal on the 3rd day of hospitalization (Video 3). At discharge (day 7), ST segment depression in D1, aVL, V5, and V6 and T negativity were maintained with normal QRS and QTc durations. An electrophysiological study was recommended for the patient.

DISCUSSION

Propafenone can provoke the development of congestive heart failure with a negative inotropic effect (1). In cases of acute toxicity, cardiovascular deterioration is observed mainly in the form of hypotension, convulsion, bradycardia, ventricular arrhythmias, QRS widening, and heart blocks (6). In this case, it was the first time being described propafenone toxicity and the development of TC accompanied by cardiogenic shock after ingestion of 600 mg of propafenone orally. Typical propafenone-related ECG changes have supported TC was dependent on propafenone use. Since it was learned that the patient had taken normal doses of propafenone and more than two hours had passed since the use of the drug, gastric lavage, activated charcoal, or aspiration was not performed. Temporary pacemaker implantation was not required as her condition improved with medical treatment. Sepsis, meningitis, pulmonary embolism, and acute myocardial infarction which may cause confusion and hypotension were not considered, since troponin, D-dimer, C-reactive protein, brain tomography, and magnetic resonance imaging were close to normal limits. There was no increase in troponin in our case. It has been reported that 10% of TC patients do not have an increase in troponin (4). Interestingly, it is observed that there is no increase in troponin in almost all TC patients developing secondary to drug use.

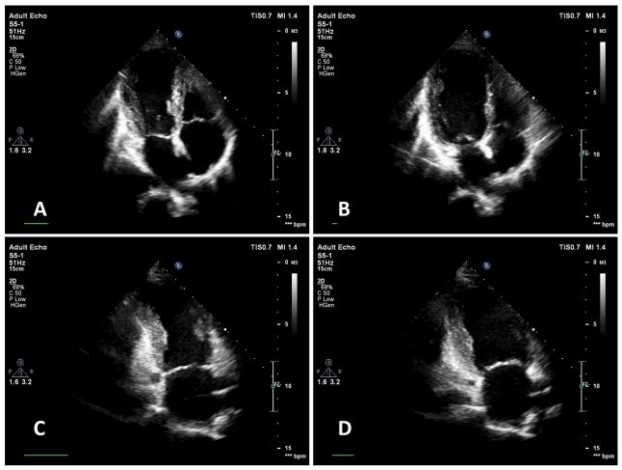


Figure 2. Transthoracic echocardiography, apical view **A)** 4 chamber, left ventricular apex aneurysmatic basal segment hyperkinetic, **B)** 4 chamber, normalized, **C)** 2 chamber, left ventricular apex aneurysmatic basal segment hyperkinetic, **D)** 2 chamber, normalized

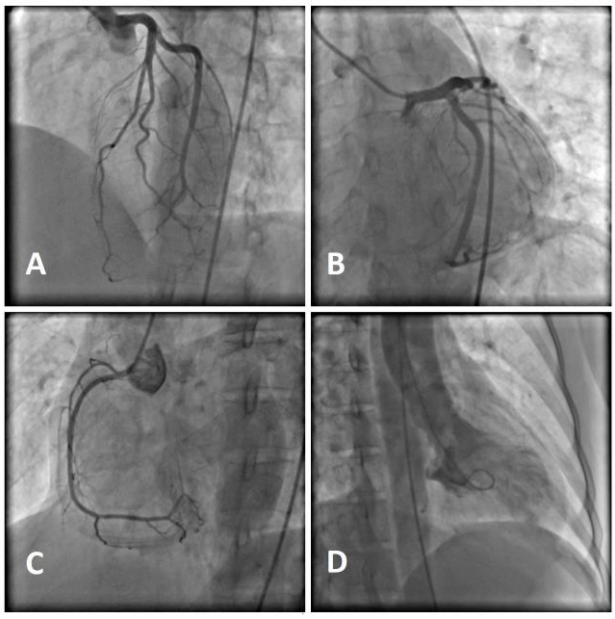


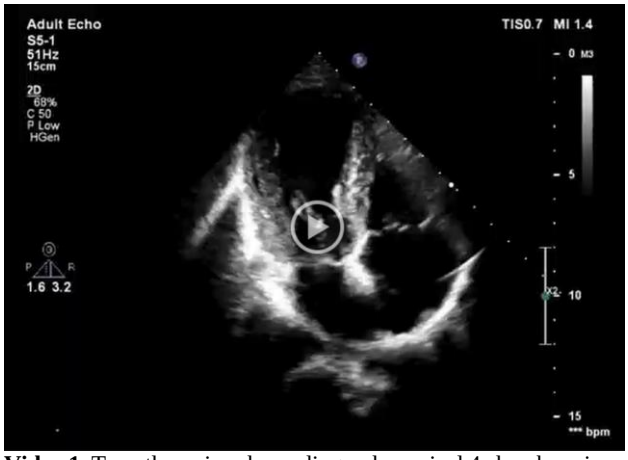
Figure 3. A, B, C) Coronary angiography of normal coronary arteries, **D)** ventriculography left ventricular apex aneurysmatic basal segment hyperkinetic

It is known that propafenone plasma concentrations may increase through inhibition of cytochrome P450 2D6. Due to the low bioavailability, steady-state and/or peak concentrations of propafenone may increase significantly in the presence of a cytochrome P450 inhibitor. Assuming a 10% to 30% bioavailability, complete inhibition of 2D6 metabolism can increase propafenone levels by up to 3 to 10 times (7). Acute toxicity has been reported between the range of 675 mg daily therapeutic dosage to 8.1 g one-time ingestion (7,8).

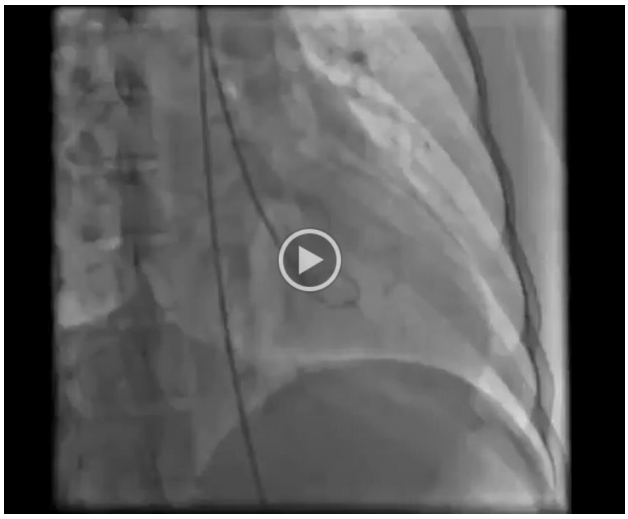
As the facility did not have the necessary equipment to measure the serum propafenone level, the diagnosis of propafenone toxicity could not be made quantitatively. However, the clinical condition of the patient at the time of admission, the absence of electrolyte imbalance, the observed ECG changes, and the fact that she did not use any medication other than propafenone focused us on this diagnosis. Opinions are controversial about the necessity of measuring serum propafenone levels in cases of acute toxicity. The patient's recovery with sodium bicarbonate administration and positive inotropic supportive treatment, which was applied with a pre-diagnosis of acute toxicity, strengthened the diagnosis. The exact incidence of such complications at therapeutic doses, especially at first use, is unknown. The possibility of such complications even at this dose is an important point to be kept in mind during propafenone use.

Propafenone can trigger heart failure by blocking sodium channels in cardiomyocytes (9). For this reason, it is not recommended in patients with heart failure. Viland et al. (10) reported a case of TC due to flecainide overdose in support of our case. Like propafenone, flecainide is also a negative inotropic anti-arrhythmic drug blocking Na^+ channels in cardiomyocytes. These cases show that Na^+ channel blockade in cardiomyocytes may play a role in TC pathogenesis. The ECGs of the case of Viland et al. (10) are similar to our case. Both cases were admitted to the emergency service with cardiogenic shock and clinical manifestation of TC. Although propafenone was taken at a normal dose in our case, flecainide was taken in toxic doses in the case of Viland et al. (10). Therefore, their case was more aggressive. The case was intubated and developed pulmonary edema, and the length of hospitalization was longer (7 days vs. 17 days).

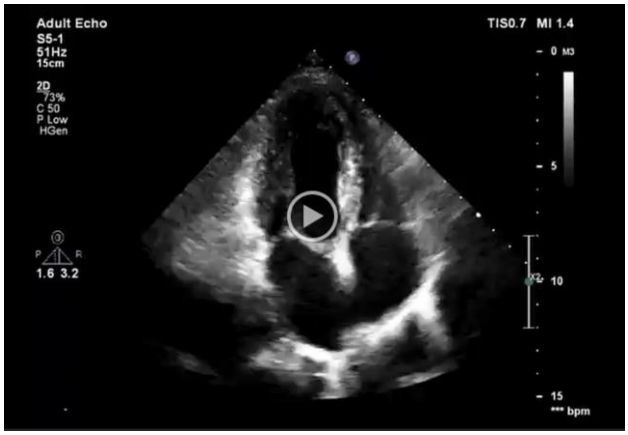
Since propafenone's affinity for sodium channels decreases at high pH levels and exhibits competitive binding on sodium channel, sodium bicarbonate application is widely recommended in the treatment (11). Another important point was not to use high-dose prolonged positive inotropic agents. In this case, we used dopamine as a positive inotropic agent with close monitoring to find the proper dosage to maintain blood pressure and hemodynamics normal and ceased as soon as possible. As TC can occur due to high catecholamines and positive inotropic agents, using these agents as they were merely needed is crucial.



Video 1. Transthoracic echocardiography, apical 4 chamber view, left ventricular apex aneurysmatic basal segment hyperkinetic



Video 2. Ventriculography left ventricular apex aneurysmatic basal segment hyperkinetic



Video 3. Transthoracic echocardiography, apical 4 chamber view, normal left ventricular systolic function

Brugada pattern and acute ST-segment elevation myocardial infarction-like ECG development secondary to propafenone intake has been reported (12-18). The detection of the Brugada pattern and acute inferior ST-segment elevation myocardial infarction-like ECG in the ECG follow-ups of our case supports the current publications. Although Brugada-like ECG changes have generally been reported with propafenone intake above therapeutic doses, there are publications reporting that this pattern can also be observed in therapeutic doses (15,17). A Brugada type 1 ECG pattern was observed but the patient did not meet any clinical criteria for Brugada Syndrome. Therefore, these changes were attributed to propafenone-induced Brugada phenocopy.

Due to the first-pass hepatic elimination effect, bioavailability is not predictable and the elimination half-life of propafenone varies depending on whether the patient's metabolizing pathways are weak or vigorous (18-20). These individual differences and important clinical changes necessitate close ECG follow-up after propafenone initiation. Especially, having the history of achieving a therapeutic effect with very high or very low doses for a disease is another important point that the toxic effects of propafenone in these individuals may occur at lower doses.

CONCLUSION

Propafenone, a medication preferred for arrhythmia control in cases where cardiac functions are known to be normal, can lead to fatal outcomes in sensitive individuals. Even though the goal is treatment, individuals taking it should be cautioned about potential side effects and worsening of their clinical condition at the beginning of treatment. On the other hand, TC is a trending clinical condition and should be always considered when inconsistent cardiac disturbances and arrhythmias cannot be explained by routine clinical reasons.

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