CASE REPORT

Modafinil-induced ventricular arrhythmia: A case report

Modafinil kullanımına bağlı ventrikül aritmisi: Olgu bildirisi

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Summary– Modafinil is a central nervous system stimulant that promotes wakefulness and is approved for the treatment of narcolepsy and several other conditions. However, there is a big concern about drug abuse, especially among students to enhance cognitive performance and to reduce the need for sleep. In this case report, we present a 23-year-old female admitted to the cardiology outpatient clinic owing to recurrent palpitations. She stated that she started modafinil 100 mg twice a day one month earlier to increase performance while studying for her exams. Her electrocardiogram (ECG) demonstrated sinus rhythm and a right bundle branch block (RBBB). No structural heart disease or metabolic pathology was detected. A 24-hour ambulatory ECG record showed 11 attacks of non-sustained ventricular tachycardia (NSVT), the longest of which was eight beats. The drug was discontinued and two weeks later, the patient was symptom-free, and her control ECG showed normal sinus rhythm with no RBBB. A control ambulatory ECG was performed, and no ventricular tachycardia was observed. Modafinil, which is considered safer than amphetamine derivatives in terms of cardiovascular side effects, rarely causes serious arrhythmic events, even in healthy subjects. Thus, we suggest evaluating patients for cardiac symptoms after starting on modafinil, and they should be also interrogated regarding the abuse of this drug.

Özet– Modafinil, bir santral sinir sistemi stimülanı olup uyanıklık indüklenmesi amacıyla narkolepsi hastalarında ve çeşitli diğer durumlarda kullanılmaktadır. Fakat bu durum için en önemli endişe kaynağı bu ilacın özellikle öğrenciler arasında kognitif performansı arttırmak ve uyku ihtiyacını azaltmak için kötüye kullanımı olmaktadır. Bu vaka takdiminde, kardiyoloji polikliniğine çarpıntı sebebiyle başvuran ve sınav performansını arttırmak amacıyla 1 ay önce günde iki defa 100 mg modafinil tablet alan 23 yaşında kadın bir hasta sunulmaktadır. Hastanın elektrokardiyogram'ında (EKG) sinus ritmi ve sağ dal bloğu saptanmış olup herhangi bir yapısal kalp hastalığı veya metabolik patoloji saptanmamıştır. 24 saatlik ambulatuvar EKG'de 11 defa tekrarlayan en uzunu 8 atımlık 11 adet süreksiz ventriküler taşikardi atakları saptanmıştır. İlacın bırakılmasını takiben 2 hafta sonrasında hastada semptom olmadığı, kontrol EKG'sinde normal sinus ritmi ve sağ dal bloğunun gerilemiş olduğu saptanmıştır. Kontrol ambulatuvar EKG'de ventriküler aritmi gözlenmemiştir. Modafinil'in amfetamin türevlerine göre kardiyovasküler yan etkiler üzerinde daha güvenli olduğu düşünülmesine rağmen sağlıklı insanlarda da nadiren ciddi aritmik olaylara yol açabilmektedir. Bu sebeple, modafinil başlandıktan sonra hastalarda kardiyak semptomların araştırılmasını ve bu ilacın kötüye kullanımı konusunda sorgulanmalarını önermekteyiz.

Modafinil is a non-amphetamine central nervous system (CNS) stimulant with wakefulness-promoting properties and approved for the treatment of narcolepsy, sleep work shift disorder, and obstructive sleep apnea. Modafinil has also been used for several additional indications such as attention-deficit/hyperactivity disorder, cocaine dependence, and various fatigue syndromes.[1] However, there is a big concern about drug abuse especially among students to enhance cognitive performance and to reduce the need for sleep. Common cardiovascular side effects of modafinil overdose include sinus tachycardia, chest pain, and hypertension.[2] Here, we present a rare cardiovascular event after modafinil abuse, non-sustained ventricular tachycardia (NSVT) and transient bundle branch block.

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A 23-year-old female was admitted to the cardiology outpatient clinic with recurrent palpitations and nausea that started one week earlier. Her past medical history was unremarkable. She denied using alcohol, tobacco, or any illegal substances. No other symptoms

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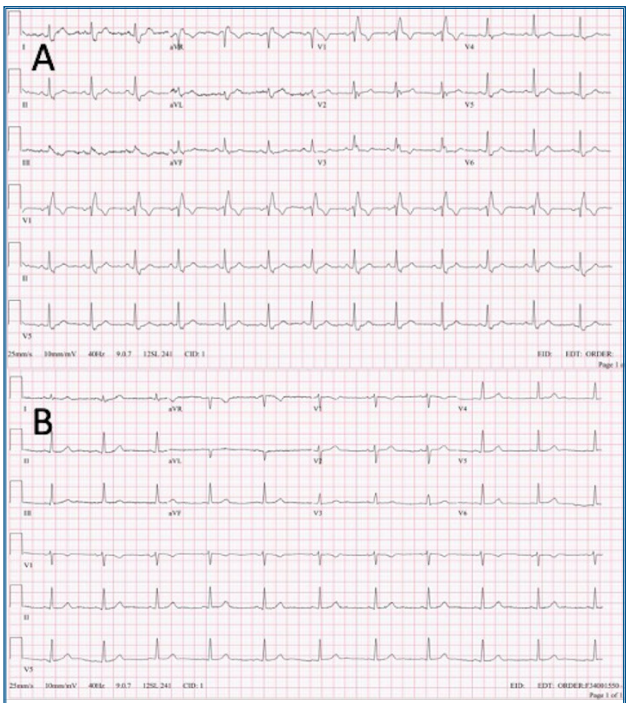

Figure 1. (A) Electrocardiogram showing normal sinus rhythm with right bundle branch block (RBBB); **(B)** regression of RBBB after cessation of modafinil.

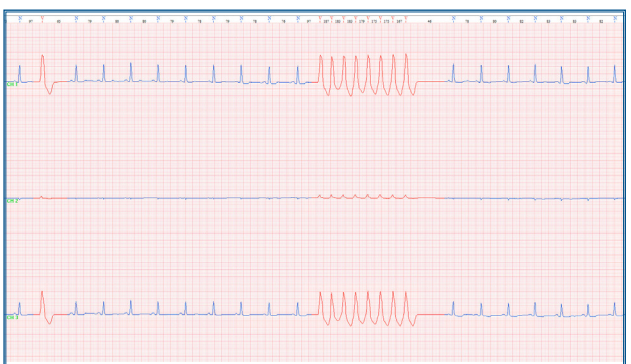

Figure 2. Recording of the 24-hour ambulatory electrocardiogram demonstrating a short run of monomorphic non-sustained ventricular tachycardia of eight beats.

were described such as angina, sweating, or dyspnea. She stated that she started modafinil 100 mg twice a day one month earlier to increase academic performance when studying for her exams. She did not use any concomitant drug. In her physical examination, she was alert, awake, and oriented to date, place, and person. She was agitated, and her rate of speech was mildly elevated. No delusions or other involuntary psychotic symptoms were detected. There was no pathology found in her cardiac and neurologic examinations. Her complete blood count and biochemical parameters were within the normal ranges. Her electrocardiogram (ECG) demonstrated a sinus rhythm and right bundle branch block (RBBB) (Figure 1A). Subsequently, a transthoracic echocardiography was performed, which showed a left ventricular ejection fraction of 60% and trace mitral regurgitation. No structural heart disease was observed. A 24-hour ambulatory ECG (Holter monitorization) showed 12,868 monomorphic premature ventricular contractions (PVC) including occasional bigeminy, trigeminy, quadrigeminy, and couplet waves. Moreover, NSVT attacks, the longest of which were eight beats, were detected 11 times (Figure 2). Modafinil was discontinued. Two weeks later, the patient was symptom-free, and her control ECG showed normal sinus rhythm with no RBBB and PVCs (Figure 1B). According to her first-month control ambulatory ECG, there were 86 PVCs recorded, and no NSVT was observed.

Abbreviations:

CNS	*Central nervous system*
DAD	*Delayed after-depolarization*
ECG	*Electrocardiogram*
FAERS	*Food and Drug Administration Adverse Event Reporting System*
NSVT	*Non-sustained ventricular tachycardia*
PVC	*Premature ventricular contraction*
RBBB	*Right bundle branch block*

Written informed consent was obtained from the patient for the publication of the case report and the accompanying images.

DISCUSSION

Modafinil is used to induce wakefulness in the treatment of narcolepsy, sleep work shift disorder, and obstructive sleep apnea. Its mechanism of action involves inhibition of dopamine and norepinephrine transporters; the elevation of extracellular catecholamines; and indirectly modulating serotonin, histamine, gamma-aminobutyric acid, and glutamate levels.[3] Compared with traditional stimulants, such as amphetamine derivatives, modafinil has shown less effect on the cardiovascular system.[4] Adverse cardiovascular effects of modafinil overdose include chest pain, sinus tachycardia, and hypertension.[2] In regular doses, modafinil has been reported to cause frequent PVCs.[5]

In healthy non-sleep deprived adults, modafinil can enhance executive function, learning, memory, and have a little effect on creativity.[6] However, there is a public health threat regarding modafinil abuse,

especially among students to boost academic performance and to reduce the need for sleep. Our case report proves even an ostensibly harmless agent can lead to life-threatening arrhythmia. Therefore, the distribution of this medicine should be regulated.

The mechanism of PVCs varies among the multiple studies conducted; however, three pathophysiological theories are widely accepted.[7] The most common one is defined as the triggered activity that is caused by after-depolarizations.[7] These fluctuations are mediated by abnormally increased intracellular calcium level, which provides a basis for PVCs and NSVTs. Delayed after-depolarization (DAD) occurs during the repolarization process of the membrane potential.[7] The most common causes of DAD are digitalis toxicity, catecholaminergic polymorphic ventricular tachycardia, and caffeine overdose.[7] Some studies have found a link between the amphetamine-like CNS stimulants and intracellular calcium imbalance, which can cause DAD and induce tachycardia.[8] Among the various properties of CNS stimulants, sympathetic receptor upregulation plays an essential role in causing tachycardia.[8] By stimulating the sympathetic receptors, cyclic adenosine monophosphate regulated phosphorylase kinase A activation leads to an increase in intracellular calcium and creation of oxidative stress.[8] An abnormally increased level of apoptosis, necrosis, and mitochondrial dysfunction could be an explanation of the myocardial dysfunction and bundle branch block as a consequence of the preternatural oxidative stress.[7,8]

The mechanism of RBBB in this patient was puzzling owing to the fact that no structural heart disease could be found. The most rational explanation was sympathetic activation leading to the emergence of discordant response of the right bundle. Chilson et al.[9] defined this phenomenon as a functional bundle branch block. In the event of increased heart rate, relative refractoriness of the right bundle can be shorter than left bundle. Therefore, RBBB can occur even in healthy people.

Binnenmars et al.[10] reported a patient who experienced polymorphic NSVT related to modafinil treatment for narcolepsy. This patient had hypertension and chronic obstructive lung disease and was thoroughly evaluated for the etiology of the arrhythmia. After discontinuation of the medicine, NSVT regressed. This case was different from our patient who did not have any systemic disease. In addition, we observed a monomorphic NSVT in her ambulatory ECG along with an RBBB pattern in her ECG. No structural heart disease, excluding the modafinil use, could be found to explain the reason of the arrhythmia. However, there was one similarity between the two cases in that tachycardia regressed after discontinuation of the agent.

We also performed a database search on the United States Food and Drug Administration Adverse Event Reporting System (FAERS). FAERS is an adverse events database based on safety reports gathered by the patients, industry, and healthcare workers. Our FAERS search revealed eight cases of VT that had not been published in the literature, two of which resulted in death.[11] However, as this database relies on individual patient data, it has a potential for bias for the causal relationship between exposure to the product and the reported event.

We thoroughly investigated our patient and excluded other common causes of PVC and NSVT, such as structural heart disease and endocrine and metabolic abnormalities. After the cessation of modafinil, frequent PVCs and bundle-branch block receded. Therefore, we concluded modafinil-induced arrhythmia as our final diagnosis.

Modafinil drug abuse is increasing especially among students to enhance cognitive performance and to reduce the need for sleep. However, it is considered safer than amphetamine derivatives in terms of cardiovascular side effects and rarely causes serious arrhythmic events, especially in healthy subjects. Thus, patients should be interrogated about abuse of this drug.

Informed Consent: Written informed consent was obtained from the patient for the publication of the case report and the accompanying images.

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Anahtar Kelimeler: Modafinil, aritmi, ventriküler taşikardi, psikofarmakoloji