Seizure Triggered by Sudden Discontinuation of Pregabalin: A Case Report
Pregabalinin Aniden Kesilmesinin Tetiklediği Nöbet: Bir Vaka Raporu

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ÖZET

Pregabalin günümüzde ağrı, anksiyete bozuklukları ve parsiyel nöbetlerin tedavisinde kullanılmaktadır. Ayrıca pregabalinin rahatlatıcı ve öforik bir etkisi vardır. Bu nedenle sıklıkla kötüye kullanılır. Pregabalin bağımlılığının tedavisi için kesin bir kılavuz yoktur. Bu olgu sunumunda, pregabalin bağımlılığı tedavisinde hastanın kullandığı yüksek doz pregabalinin ani kesilmesi sonucu sağlıklı bir yetişkinde epileptik nöbet ortaya çıkması anlatılmaktadır. Literatürde benzer bir olguya rastlanılmamıştır.

Anahtar Kelimeler: Yüksek doz pregabalin, pregabalin kesilmesi, kesilme nöbeti

ABSTRACT

Pregabalin is currently used in the treatment of pain, anxiety disorders and partial seizures. Pregabalin also has a relaxing and euphoric effect. For this reason, it is frequently abused. There is no definitive guideline for the treatment of pregabalin addiction. This case describes the emergence of an epileptic seizure in a healthy adult with the sudden discontinuation of high-dose pregabalin in the treatment of pregabalin addiction. In the literature, no similar case has been reported.

Keywords: High dose pregabalin, pregabalin discontinuation, discontinuation seizures

Introduction

Pregabalin is a gamma-aminobutyric acid analog used to treat pain, anxiety disorders, and partial seizures; it is also used off-label for conditions such as insomnia, fibromyalgia, and restless legs syndrome (1, 2). In addition to its therapeutic use, it also has euphoric and relaxing effects, and for this reason, pregabalin is often misused or abused (2). In recent years, many studies have been reported from different countries about pregabalin abuse and dependence (3-5).

In this case report, we present a patient with pregabalin dependence who was experienced tonic-clonic epileptic seizures following the sudden withdrawal of pregabalin. There are some cases in the literature of epileptic patients experiencing seizures after discontinuation of pregabalin (6-8). However, our case differs from other cases in the literature because there is no case of a healthy individual with no history of epilepsy experiencing an epileptic seizure after discontinuation of high-dose pregabalin. It is also important to note that pregabalin should not be stopped abruptly in the treatment of pregabalin addiction. Informed consent has been obtained from the patient for the publication of this case.

Case Presentation

A 24-year-old male patient applied to the Alcohol and Drug Detoxification Center, stating that he had been abusing pregabalin for 2 years. The patient stated that he had started abusing pregabalin at the age of 20, and that sometimes (average 2-3 times a month) he added substances such as cannabis and methamphetamine (last used any of these 5 months ago). Initially, he used 4-6 tablets orally (300 mg tablets) per day. Over time, with the induction of stressful life events, the amount of use gradually increased, and he stated that he had been using 14 pregabalin tablets per day (4200 mg/day) for the last two years. He decided to quit pregabalin and stopped it completely 2 days before admission. On the first day after discontinuation (Day 1), he began experiencing withdrawal symptoms. The day after stopping pregabalin, he began experiencing withdrawal symptoms such as body aches, restlessness, insomnia, and angry outbursts. Unable to tolerate these symptoms, he presented to the outpatient clinic on Day 2 to manage these symptoms. The treatment was initiated with venlafaxine (extended-release form) 75 mg/day, quetiapine 100 mg/day, and diclofenac potassium 150 mg/day on the day of admission (Day 2). Physical examination, vital signs, and laboratory tests were within normal limits. Depressed mood, anxiety, impaired attention and concentration, and increased psychomotor activity were determined in a psychiatric examination. The patient had several symptoms, including autonomic hyperactivity, anxiety, and insomnia, and these symptoms started one day after stopping pregabalin; so the patient was diagnosed with sedative, hypnotic, or anxiolytic withdrawal according to DSM-5. The patient was hospitalized in a detoxification clinic to manage these symptoms. Treatment was initiated with venlafaxine (extended-release form) 75 mg/day, quetiapine 100 mg/day, and diclofenac potassium 150 mg/day. The patient had a generalized tonic-clonic seizure on the third day of being off pregabalin, which was also the second day of hospitalization (Day 3). The seizure was treated with a single dose of 5 mg intramuscular diazepam (intravenous administration was not possible due to contractions). The patient had no history of seizures. No abnormalities were detected in the laboratory tests (electrolytes, glucose, toxicology, infection markers, etc.) The neurological examination, brain MRI, and EEG were reported to be all normal. As a result of the neurology consultation, it was recommended that the pregabalin dose be reduced and gradually discontinued. The patient was started on 300 mg/day of pregabalin, and 25 mg was tapered daily. Pregabalin withdrawal symptoms subsided by the end of the third day of hospitalization.

No seizures were observed during the remainder of the hospitalization or at one year of outpatient follow-up.

Discussion

The prevalence of gabapentinoid abuse is 1.6% in the general population, and prevalence among substance abusers ranges from 3% to 68% (9). There is a lot of data in the literature about the side effects and toxicity of pregabalin. However, there are few case reports and studies on pregabalin withdrawal symptoms. To the best of our knowledge, there is no data in the literature on the development of epileptic seizures with the sudden discontinuation of pregabalin in a healthy individual without a history of epilepsy.

Some neurological side effects, including epileptic seizures, have been reported with PGB abuse. High doses of pregabalin, an anticonvulsant drug, can cause neurotoxicity through increased oxidative stress, dysregulation of neurotransmitter release, antioxidant depletion, brain tissue inflammation, and stimulation of apoptotic mediators. In animal models, high-dose pregabalin administration disrupts p38 mitogen-activated protein kinase (p38-MAPK) signaling, leading to neuronal hyperexcitability (6). Acute or chronic toxicity of pregabalin results in encephalopathy that may cause overt seizures or epileptiform activity, with EEG findings including stationary triphasic waves (TW) and slow background activity, characteristic of toxic metabolic encephalopathy (7). However, pregabalin-induced seizures are benign and self-limiting (7).

Different mechanisms may play a role in the pathophysiology of seizures during pregabalin withdrawal. First, the sudden cessation of pregabalin's blockade of presynaptic voltage-gated calcium channels leads to a surge of calcium influx, causing excessive release of excitatory neurotransmitters, most notably glutamate. Second, chronic pregabalin use leads to adaptive downregulation of GABAergic inhibition and upregulation of glutamatergic excitation. The drug's abrupt discontinuation unmasks this imbalance, creating a state of net hyperexcitability. Third, and perhaps most importantly, in the context of abuse with intermittent mini-withdrawals, repeated neuronal hyperexcitability can "kindle" the brain, leading to long-lasting hyperexcitability and lowering the threshold for future seizures.

Although the mechanism of action of pregabalin is not fully understood, it decreases calcium current by binding to the presynaptic voltage-gated calcium channel. This reduces postsynaptic excitability by decreasing excitatory neurotransmitters such as glutamate, serotonin, noradrenaline, and substance P. Pregabalin is therefore used in pain management and as an antiepileptic. Pregabalin also increases extracellular GABA levels and is responsible for this euphoric and relaxing effect (10-12). Withdrawal symptoms of pregabalin have been reported as insomnia, headache, nausea, anxiety, diarrhea, dizziness, irritability, and convulsions (13-15). In studies conducted in the current literature, a case of seizure development after pregabalin withdrawal in a patient with renal failure has been reported, but no report of seizure development after pregabalin withdrawal in a healthy individual has been found (15).

Antidepressants such as venlafaxine are known to cause epileptic seizures. Our patient's seizure occurred on the second day of venlafaxine treatment. The time to reach steady-state concentration for venlafaxine is approximately 3 days (16). It is important to note that the pro-convulsant risk of antidepressants is often highest during the initial treatment phase or dose escalation, due to the rapid perturbation of monoaminergic systems. However, the temporal relationship between the seizure and the pregabalin withdrawal timeline (occurring 3 days after the last dose) is highly characteristic of sedative-hypnotic withdrawal seizures. Furthermore, the patient had no further seizures during the remainder of the one-month hospitalization,

despite continued venlafaxine treatment. Therefore, we consider venlafaxine to be an unlikely primary cause, though a potential contributory factor cannot be entirely ruled out.

Sudden discontinuation of antiepileptic drugs may cause recurrence of seizures in people with epilepsy, even if the person has not had seizures for a long time; therefore, it is recommended to discontinue them over 6-9 weeks (17). In the present case, although the patient did not have a history of epilepsy, he had seizures. During the treatment of pregabalin abuse, gradual discontinuation was performed by decreasing the dose of pregabalin, similar to other antiepileptic drugs, and no seizure was observed in the patient during hospitalization and in the follow-up after discharge within 1 year.

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Conflict of Interest

None

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