Case report / *Olgu sunumu*

Gabapentin withdrawal in a depressed patient: A case report

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ABSTRACT

The third generation antiepileptic, gabapentin, is a structural analogue of gamma aminobutyric acid (GABA), which is an important neurotransmitter of central nervous system. It is used to treat partial epilepsy, neuropathic pain, and movement disorders, as well as a variety of psychiatric conditions such as bipolar disorder, anxiety disorder, and alcohol addiction. Currently it is accepted to possess a potential for abuse and addiction. In this study, we present a case of a woman with depression who had been using a high dose gabapentin treatment for neuropathic pain due to spinal surgery performed 3 years before. Here, we highlight the withdrawal symptoms following the termination of gabapentin, and their treatment. The symptoms of varying severity in gabapentin withdrawal underline the importance of progressively decreasing the dose on a schedule of several months before ceasing the drug completely. Predisposing factors should be noted, and alternative treatment options like melatonin and mirtazapine should be considered. ***(Anatolian Journal of Psychiatry 2016; 17(Suppl.3):61-63)***

Keywords: *gabapentin, withdrawal, drug abuse*

Bir depresyon hastasında gabapentin yoksunluğu: Olgu sunumu

ÖZ

Gabapentin santral sinir sisteminin önemli bir nörotransmitteri olan gamma amino bütirik asitin (GABA) yapısal analoğu üçüncü kuşak bir antiepileptiktir. Parsiyel epilepsi, nöropatik ağrı ve hareket bozuklukları tedavisinin yanı sıra bipolar bozukluk, anksiyete bozukluğu ve alkol bağımlılığı gibi psikiyatrik hastalıkların tedavisinde kullanıldığını bildirilmiştir. Günümüzde kötüye kullanım ve bağımlılık potansiyeli olduğu da kabul edilmektir. Olgu sunumumuzda depresyon tanısı ile izlenen ve üç yıl önce geçirdiği vertebra cerrahisine bağlı olarak gelişen nöropatik ağrılar nedeniyle yüksek doz gabapentin kullanan bir kadın hastada, gabapentinin kesilmesiyle birlikte ortaya çıkan yoksunluk belirtilerini ve tedavi sürecini ele aldık. Gabapentin yoksunluğunda tanımlanan değişen şiddetteki belirtiler tedavinin doz azaltılarak ve ayları bulan uzun süre içinde sonlandırılmasının önemini ortaya koymaktadır. Gabapentin çekilme belirtileri varlığında predispozan etkenler dikkate alınmalı, melatonin ve mirtazapinin bir tedavi alternatifi olarak düşünülebileceği akılda bulundurulmalıdır. ***(Anadolu Psikiyatri Derg 2016; 17(Ek.3):61-63)***

Anahtar sözcükler: *Gabapentin, yoksunluk, madde kötüye kullanımı*

INTRODUCTION

The antiepileptic agent, gabapentin, is a structural analogue of gamma aminobutyric acid (GABA), which is the inhibitory neurotransmitter of brain.[1] Although not entirely clear, its mechanism of action is assumed to be through reducing the postsynaptic excitation by binding to the α-2 ligand subunit of the voltage dependent calcium channels, thus inhibiting the neurotransmitter release.[2] In addition, it may increase the GABA levels by enhancing the glutamic-acid-decarboxylase enzyme activity, the enzyme which is responsible for GABA synthesis.[3,4] Gabapentin is absorbed primarily in the small intestine. Peak plasma level is reached 2-4 hours after digestion, with a half-life of 5-7 hours. The drug crosses the blood-brain barrier via binding to specific L-amino acids. It neither is metabolized in the liver and bio-transformed, nor effects the

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metabolism of other drugs.[5]

Having a lower side-effect potential and a wide therapeutic range due to drug interactions, gabapentin is used for multiple indications, such as epilepsy, neuropathic pain, bipolar disorder, migraine, and alcohol withdrawal.[6,7] In addition to its GABA-mimetic properties, it is also accepted to exert direct or indirect effects on the dopaminergic reward system.[8,9] Currently, it is assumed to possess a potential for abuse and addiction.[10] This report presents a case with withdrawal symptoms after termination of high dose gabapentin medication and summarizes the treatment process.

CASE

A 38-year-old woman had been taking gabapentin treatment at a dose of 1600-4000 mg/day, for three years for neuropathic pain that occurred after spinal surgery. She had become temporarily bedbound after the surgery, and had been taking 150 mg/day venlafaxine for depression for two years. After the treatment, she was mobilized and returned to work. She stated that she had been benefitting from the euphorizing effects of gabapentin, and she had realized that those effects had been diminishing day-by-day, giving rise to a need for even higher doses. However, due to its negative effects on her cognitive functions, she had gradually reduced the doses of gabapentin on a schedule of one month, and ceased the drug completely by then. She admitted to our psychiatry clinic with nausea, fatigue, sweating, palpitation, excitability, and increase in anxiety, insomnia, and generalized pruritus with an onset within 24 hours after stopping gabapentin. She was taking 150 mg/day venlafaxine and 1-3 mg/day alprazolam, but without any relief of her symptoms. Her vital signs and laboratory results (complete blood count, biochemistry, and thyroid function tests) were within normal ranges. Her Beck Depression Scale score was 9. Her functional status was normal. Her medical history revealed a depression six years ago, and several other spinal surgeries. She denied any substance abuse, and she did not have any neurological and internal medical problems. Her family history did not reveal any psychiatric disorders. As the symptoms were suggestive of gabapentin withdrawal, re-initiation of the medication was suggested. However, the patient refused taking the drug for its addiction potential. A 5 mg/day melatonin treatment was added, achieving a reduction in anxiety levels and an ease in sleep initiation, as stated by the patient. However, for the persistence of the symptom set, 15 mg/day mirtazapine was prescribed. One week later, pruritic symptoms were reduced and gastrointestinal complaints and insomnia disappeared. On the follow-up visit after one month, the patient described very mild residual symptoms on rare occasions, which she easily tolerated.

DISCUSSION

Gabapentin, which has a GABA-related activity, may lead to abstinence symptoms through unclear mechanisms. Case studies report that these symptoms occur in patients who are given daily gabapentin doses of 400-8000 mg,[11] with an onset within 12 hours-7 days after termination of the drug.[12] Withdrawal symptoms may mimic those of alcohol and benzodiazepine, which has a GABA-related mechanism of action.[11] Reported gabapentin withdrawal symptoms include sweating, tachycardia, gastrointestinal symptoms, anxiety, agitation, confusion, catatonia, and epileptic seizures.[6,7] Our case had sweating, tachycardia, gastrointestinal symptoms, insomnia, irritability, and anxiety. At the time of her admission, she had already been taking alprazolam 1-3 mg/day, for one week; nevertheless, her symptoms had persisted despite this medication. Thus, benzodiazepine treatment may be deemed ineffective in our particular case of gabapentin withdrawal. This may be related to the fact that gabapentin (a synthetic presynaptic modulator of voltage dependent calcium channels) and benzodiazepines (acting through postsynaptic GABAA receptors) exert their effects through distinct mechanisms. The presence of premorbid-comorbid depression in our case might have acted as a predisposing factor for gabapentin withdrawal. A previous case report presented a 75-year-old patient with recurrent depression, in whom symptoms such as sweating, chills, and abdominal pain showed up 24 hours after ceasing of gabapentin treatment.[10] Another case report of a woman taking 1500 mg gabapentin a day for bipolar disorder described catatonia as a symptom of gabapentin abstinence.[13] Gabapentin replacement cures the symptoms of abstinence in the majority of cases. Our patient refused to re-initiate gabapentin, besides alprazolam was ineffective in relieving her symptoms. Instead of abruptly terminating gabapentin, she had gradually decreased the dose of the drug for one month, possibly contributing in tolerating the withdrawal symptoms. There are three cases described in the literature,

in whom the abstinence symptoms spontaneously disappeared in time, without any medication.[12] In one of these cases, a 35-year-old woman using 3600 mg/day gabapentin, the treatment was ceased gradually in 6 weeks' time, and her abstinence symptoms (headache, chills, sweating, and gastrointestinal cramps) cleared without any treatment. In our case, we stopped alprazolam and started melatonin 5 mg/day, and mirtazapine 15 mg/day. After one week, nausea, sweating, tachycardia, and fatigue symptoms were completely gone, anxiety and irritability symptoms were significantly reduced, and pruritus persisted with a small alleviation.

Studies on melatonin, a hormone of the pineal gland, demonstrated that it has anxiolytic and sedating effects. These effects of melatonin are thought to be GABAergic-system-related, possibly through a similar pathway with benzodiazepines.[14] Without any clear explanations, our patient benefited from the anxiolytic effects of melatonin, but not benzodiazepines.

Mirtazapine is an atypical antidepressant that accelerates the transmission of monoamines. Its action is mediated through multiple receptors. It is an antagonist of the norepinephrine α_2 and serotonin $5HT_2A/C$ receptors, and an inverse agonist of the $5HT_2C$ receptors. A 2009 study on rats, which investigated the behavioral patterns in the etiology of addiction, demonstrated that mirtazapine reduced the morphine withdrawal symptoms by regulating monoamine transmission, and might help maintaining abstinence in opioid addiction.[15]

Our patient benefitted from melatonin and mirtazapine combination. Melatonin may be an alternative to benzodiazepines, and mirtazapine may be effective in alleviating the symptoms of gabapentin withdrawal.

CONCLUSION

The symptoms of varying severity defined in gabapentin withdrawal underline the importance of progressively decreasing the dose on a schedule of several months, before ceasing the drug completely. In the presence of gabapentin withdrawal symptoms, possible predisposing factors must be considered. Alternatively, melatonin may be prescribed in higher doses in that it does not have any abuse potential. Mirtazapine, which is an atypical antidepressant, should also be considered as an option.

Yazarların katkıları: *B.Y.: Konu seçimi, literatür tarama, makale yazma; H.B.E.: Literatür tarama, planlama, gözden geçirme.*

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