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Pregabalin Intoxication in a Patient with Heroin Addiction

Emine Aslanlar, Zeynep Cura, Mehmet Sari, Ahmet Sonmez, Jale Bengi Celik, Ozkan Onal*
Medical Faculty, Department of Anesthesia and Reanimation, Selcuk University, Turkey

Case Report

***Corresponding author**
Ozkan Onal

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Abstract: Pregabalin is an anticonvulsant which is an analog of gamma-aminobutiric. It increases normal GABA levels by binding to α2-δ subunit in voltage sensitive calcium channels and inhibiting excitator neuro-transmitter release. It exerts analgesic and anxiolytic effect by decreasing the release of neurotransmitters such as glutamat, noradrenalin and substance P. It is used for treatment of neuropathic pain, fibromyalgia, generalized anxiety disorder, epilepsy, and benzodiazepine and alcohol dependence. The most marked affect stated by users of Pregabalin is euphoria. It is known that, it has a potential of misuse, due to this effect and leads to dependence. The addicts use high doses Pregabalin for getting euphoria effect. The majority of Pregabalin addicts are known to misuse at least one other psychoactive substance or drug previously.We presented a patient with heroin addiction who started to use high dose Pregabalin for recreational purposes. We wanted to draw attention to that pregabalin misuse by itself and in combination should be borne in mind in case of intoxication and effects such as prolonged sinusal bradycardia
Keywords: Pregabalin, , euphoria, misuse, prolonged sinusal bradycardia.

INTRODUCTION

Pregabalin, is an anticonvulsant which is an analog of gamma-aminobutiric acid. It was discovered in Northwestern University as an antiepileptic drug, but subsequently it was understood to be effective only on partial convulsions [1]. It increases normal GABA levels by binding to α2-δ subunit in voltage sensitive calcium channels and inhibiting excitator neuro-transmitter release.

It exerts analgesic [1-4] and anxiolytic effect [5,6] by decreasing the release of neurotransmitters such as glutamat, noradrenalin and substance P [5,6]. When used orally, it is absorbed rapidly and bioavailability is over 90% irrespective of the dose. Only a small portion is metabolized in the liver and 98% is excreted with urine without being metabolized. Elimination half life is 5.5-6.7 hours independent of dose and repeated doses. Although it is generally well tolerated, side effects such as somnolence, vertigo, visual blurring, asthenia, euphoria, gait imbalance and cognitive difficulties (primarily with concentration or attention), peripheral edema, dry mouth, weight gain, increased appetite and constipation may occur [7].

CASE REPORT

A 21 year old male patient who has been heroin addict for last five years and has used many recreational substances meanwhile discovered the side effects of pregabalin such as anxiolytic effect, euphoria and hallucination and then used high dose pregabalin (1200 mg) in combination with heroin. Subsequently, he was brought to emergency service with loss of consciousness and respiratory arrest and was admitted to intensive care unit after being intubated. At presentation, Glascow Coma Score was 3, pupillas pint point, indirect reflexes negative, heart rate was 70/min. and blood pressure 80/40 mm/hg. As blood pressure was low, noaradrenaline support treatment was initiated. No important findings were observed in electrocardiogram. Brain and cervical CT imaging examination was carried out with no acute pathology. In urine investigation, urine was found to be benzodiazepin and opioid positive. Patient was followed for 48 hours under sedation. Hemodynamics was stable and respiratory distress improved. Subsequently, 12 hours after the termination of sedation, deep bradycardia refractory to atropine emerged. Heart rate was 30-40/minute. In electrocardiogram, in V1, V2 and V3 leads, ST depression was observed. Cardiology clinic was consulted for indication of pacemaker. Since sinus bradycardia was present, which does not impair hemodynamics, pacemaker was not considered. In order to bring heart rate to normal limits, low dose adrenalin infusion was recommended and administered. Patient was extubated after 72 hours and was discharged after consultation with psychiatry clinic.

DISCUSSION

In 2005, its use in neuropathic pain associated with diabetic peripheric neuropathy and fibromyalgia and in postherpetic neuralgia was approved [8]. In addition, it was also approved in 2006 for use in generalized anxiety disorder [9]. In Turkey, with the approval of the Ministry of Health, it is used at the doses of 150-600 mg/day in peripheric neuropathic pain, generalized anxiety disorder, fibromyalgia, and the treatment of adult patients with partial epilepsy. Recently, there have been studies indicating that it is effective in the treatment of benzodiazepine and alcohol dependence. Pregabalin is prescribed 150-450 mg/day for alcohol dependence, and 225-900 mg/day for benzodiazepine dependence[10]. However, there are reported cases in whom Pregabalin dependence itself developed while being used for dependency treatment.

The most marked affect stated by users of Pregabalin is euphoria. It is known that, it has a potential of misuse, due to this effect and leads to dependence [11].The majority of Pregabalin addicts are known to misuse at least one other psychoactive substance or drug previously [12-14]. Likewise, in the present case, there was five year history of heroin use and he started to use Pregabalin for recreational purposes. In a paper reporting 10 cases between the ages of 20-35 using Pregabalin at such high doses as 500-1400mg for recreational purposes, toxic effects of the drugs were stressed and it was reported that convulsion was observed in 6 patients and in 2 patients intubation and ventilation was required as in the present case [15]. There are also cases reported to have intoxication only with Pregabalin. Patients who received Pregabalin at toxic doses such as 3gr, 8.4 gr and 11.5 gr. could be treated with general support and symptomatic approach [16,17]. It is thought that general support and symptomatic approach suffices as a very large majority of the drug is excreted from kidneys without metabolization and they have functioning kidneys [16]. General support and symptomatic approach was adequate in the present case, who did not have any renal failure.

There are reports mentioning that cardiac side effects may occur even in treatment doses of Pregabalin. Murphy *etal*. [18] reported the development of decompansated heart failure associated with PRG in three patients. Laville*et al*. [19] presented an elderly case in whom atrial fibrillation and congestive heart failure developed 15 hours after the first dose of Pregabalin. Alp *et al*. [20], in their rabbit study, demonstrated that Pregabalin increased heart rate and prolonged QT interval in dose dependent manner. Hill *et al*. [21] noticed that ST elevation developed in ECG of a patient who received postoperative 300 mg Pregabalin and that elevation improved within 2 hours and thought that Pregabalin induces coronary artery spasm. Aksakal *et al*. [22], stated that in a patient with complete AV block with daily dose of 300 mg Pregabalin, block reverted spontaneously to Mobitz type 2 block 2 days after the discontinuation of drug and to right branch block sinus rhythm 7 days later. It was thought that Pregabalin, binds to α2-δ subunit of voltage sensitive L type calcium channels which are present in myocardium as in central nervous system, with high affinity, leading to these cardiac effects. This may be because L-type calcium channels are the key gateway for calcium influx into cardiac myocytes that play a key role in excitation-contraction coupling [20]. Aksakal *et al.* [22] suggested that varying effects of Pregabalin on ECG and heart may be associated with different distribution pattern of L-type calcium channels in myocardium. In the present case, noradrenaline infusion was carried out for two days owing to hypotension and after bradycardic course and deep sinusal bradycardia, low dose adrenaline infusion was initiated.

In a postmortem toxicology study performed in Finland,the rate of misuse of Pregabalin was reported to be 48.1%. Of these, in a large majority (91.4%) Pregabalin was not used on its own but was combined with opioids. They drew attention to the fact that high dose Pregabalin in combination with opioids may have lethal outcomes[23].

In patients with a history of alcohol and substance addiction, pregabalin misuse may occur. It is our suggestion that pregabalin misuse by itself and in combination should be borne in mind in case of intoxication and effects such as prolonged sinusal bradycardia.

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