CASE REPORT

SEIZURES AFTER USE AND ABUSE OF TRAMADOL

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Abstract: Seizures have been reported with tramadol monotherapy in animal and human studies, both at recommended and high doses. After tramadol abuse or overdose, neurotoxicity is speculated to be related to the reuptake inhibition of serotonin and norepinephrine, rather than its opioid effects.

THE AIM OF THIS STUDY is to show three unusual cases of seizures provoked by tramadol.

Case reports: A 56 year-old female was hospitalized with intensive lumbosacral pain. Because the standard therapy with non steroid anti-inflammatory drugs and diazepam did not show enough pain release, Tramadol ampoules were applied. Fifteen minutes later generalized tonic clonic seizure was noticed.

A 24 year-old female was admitted to the Toxicology Clinic, one hour after ingestion of 1000 mg Tramadol (20 pills of 50 mg) in a suicide attempt. Five hours later generalized tonic clonic seizure was noticed.

A 27 year-old male was hospitalized for detoxification procedure with buprenorphine. The patient was a more than four years heroin abuser, and in the last two years he mixed the heroin with high doses of tramadol. 16 hours later, after application of the first 2 mg of Buprenorphine, generalized tonic clonic seizure was noticed.

Conclusion: Tramadol prescription, use and abuse are connected with the risk of developing seizures. The neurotoxicity of tramadol commonly manifests as seizures.

Key words: tramadol, use/abuse, seizures
Introduction

"Divinum est opus, sedare dolorem" says an old Latin proverb.

Billions of dollars are spent every year on analgesics all around the world. In Australia, the cost of managing chronic pain is estimated to be $34 billion per year [1]. Given the narcotic alternatives for treatment, tramadol is a unique pharmacological bullet in the fight against chronic pain. To attest to its popularity, prescriptions for tramadol in Canada reached almost 26 million in 2006, representing total sales of $800 million [2]. Tramadol is an analgesic medication that is a synthetic analogue of codeine. In comparison with other opiates, tramadol is renowned for having less abuse potential and less respiratory depression. In terms of specific neurotransmitter effects, at the central level, tramadol is a mu-opioid receptor agonist. The affinity of tramadol for mu-opioid receptors (analgesic effect) is 10-fold less than codeine. However, the active metabolite of tramadol, o-desmethyltramadol, has a far greater affinity (up to 200-fold) than the parent compound. In addition to its central effects on mu receptors, at the peripheral level, tramadol inhibits serotonin and norepinephrine reuptake. These latter effects are likely to be an important element in analgesia, but may also account for some of the adverse properties of the drug [3]. Tramadol has many characteristics that are similar to venlafaxine, including structural similarities and serotonergic/noradrenergic reuptake inhibition [4]. Not surprisingly, using liquid chromatography to detect levels of tramadol in urine, venlafaxine may cause false positive results [5].

Seizures have been reported with tramadol monotherapy in animal and human studies, both at recommended and high doses [6, 7]. After tramadol abuse or overdose, neurotoxicity is speculated to be related to the reuptake inhibition of serotonin and norepinephrine, rather than its opioid effects. Patients with an existing seizure disorder appear to be most at risk of adverse effects [8].

The aim of this study is to show three unusual cases of seizures provoked by tramadol, treated at the University Toxicology and Neurology Clinics.
Case report 1

A 56 year-old female was hospitalized at the University Toxicology Clinic in Skopje with intensive lumbosacral pain. CT of lumbosacral vertebrae showed nerve compression on segment L[4, 5]. The standard therapy with non steroidal anti-inflammatory drugs and diazepam, applied in the first two days of hospitalization, did not show enough pain release and in the next few days a Tramadol ampoule of 100 mg two times/day was applied. 15 minutes after the fourth ampoule was applied, generalized tonic clonic seizure was noticed. The seizure was successfully treated with 5 mg intravenous Diazepam. The medication was immediately ceased and no further seizures were noticed. Brain computed tomography (CT) and magnetic resonance imaging (MRI) were normal. An electroencephalogram (EEG) showed no epileptiform activity.

Case report 2

A 24 year-old female was admitted to the University Toxicology Clinic in Skopje, one hour after ingestion of 1000 mg Tramadol (20 pills of 50 mg) in a suicide attempt. At admittance she was somnolent (Glasgow Coma Score 11), eupnoic, hypotensive (11/7 kPa). After standard detoxification procedure, saline infusions with vitamins were applied. Five hours later generalized tonic clonic seizure was noticed. The seizure was successfully treated with 10mg i.v. diazepam and continued with 2 mg tablets of Lorazepam in the next four days. The patient had no prior history of epilepsy or convulsions. The patient was discharged without any sequels or further seizures 96 hours after admittance. The further neurological examination (EEG, CT) did not show any disturbances.

Case report 3

A 27 year-old male was hospitalized to the University Toxicology Clinic in Skopje, for a standard detoxification procedure with buprenorphine. The patient had a history of more than four years as a heroin abuser, and in the last two years he mixed the heroin with high doses of tramadol (approximately 500–1000 mg two to three times weekly). No evidence of prior seizures was noted. 16 hours later, after application of the first 2 mg of Buprenorphine generalized tonic clonic seizure was noticed. The seizure was successfully treated with 10 mg i.v. diazepam, and 5 mg given orally in the next three days. Detoxification was successfully finished in the next six days, without any neurological signs. EEG did not show any abnormalities.

Discussion

We present three unusual cases of generalized tonic clonic seizures after use and acute/chronic abuse of Tramadol.
In the first case, the seizures were noticed after two days of treatment with therapeutic doses of Tramadol. According to our data base this is the first registered case of seizures after therapeutic use in the Republic of Macedonia. Few studies have analysed this phenomenon. Gardner et al. examined a cohort of more than 9,000 patients taking tramadol in a managed care population. While fewer than one percent (80) had an alleged seizure after their first prescription of tramadol, the risk increased 2- to 6-fold when adjusted for selected medical comorbidities and concomitant prescribed drugs. In an Australian study, Labate et al. found that 8.2 percent of new-onset seizures were accounted for by tramadol exposure [9, 10]. However, an additional study found no increased risk of seizures with tramadol monotherapy, and another concluded that there was no higher risk compared to other analgesic monotherapies [11, 12].

Seizures after acute poisoning with tramadol, as in our second case, are not so rare in world statistics, but this is the first case in our Clinic from the total number of 17 patients poisoned with Tramadol in the last decade. A lot of studies and case reports describe the same manifestation after acute poisoning with tramadol. Fakhroldin Taghadosi et al. in his study analyzed 400 patients intoxicated with tramadol, and found that more than 30% developed seizures [13]. In another Iranian study the percentage of the seizures after tramadol intoxications was estimated at about 46%. In the same study, the authors found no significant correlation between ingested dose and seizures [14]. The highest percentage of seizures after acute poisoning with tramadol (54,4%) was noticed in the study published in 2006 [15].

Tramadol dependence and withdrawal are not uncommon and have been reported, particularly after abrupt cessation of long-term treatment. Tramadol withdrawal resembles opioid withdrawal, however in some instances atypical neuropsychiatric symptoms including hallucinations, psychomotor agitation and confusion have been reported [16]. Seizures are not common. There is not sufficient evidence and relevant data about this, and all current knowledge is based on case reports. According to our knowledge, the third presented case is the first reported case of seizures of a patient with tramadol withdrawal syndrome, treated with buprenorphine.

**Conclusion**

Tramadol prescription is associated with the risk of developing seizures. Tramadol has relatively high potential to provoke seizures after acute overdose. Seizures may be a feature of atypical withdrawal. The neurotoxicity of tramadol commonly manifests as generalized tonic-clonic seizures.
REFERENCES


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Резиме

КОНВУЛЗИИ ПРИ УПОТРЕБА И ЗЛОУПОТРЕБА НА ТРАМАДОЛ

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Епилептичните напади се евидентирани при употреба на трамадол во студии со експериментални животни и луѓе, како во терапевтски така и во високи токсични дози. По злоупотреба или труење со трамадол, невротоксичноста се претпоставува дека е предизвикана со повратната инхибиција на серотонинот и норепинефринот, а многу помалку од опијатниот ефект.

Цел на трудот е да се прикажат три различни случаи на епилептични напади провоцирани од трамадол.

Приказ на случаи: 56-годишна жена е хоспитализирана поради лумбосакрална болка. Бидејќи стандардната терапија со нестероидни антиинфламаторни лекови и дијазепам не даде задоволителен терапевтски одговор, беа ордирирани ампули трамадол. 15 минути по апликацијата беа нотирани генерализирани тонично-клонични епилептични напади.

24-годишна жена е донесена на Клиниката за токсикологија по ингестија на 1000 mg трамадол (20 таблети по 50 mg) при обид за самоубиство. Пет часа подоцна беа регистрирани генерализирани тонично-клонични грчеви.

27-годишен маж е хоспитализиран за детоксикација со бупренорфин. Пациентот повеќе од четири години е героински корисник, а последните две години героинот го комбинира со високи дози на трамадол. 16 часа по внесот на 2 mg бупренорфин регистриран е интензивен генерализиран тонично-клоничен епилептичен напад.

Заклучок: Употребата и злоупотребата на трамадол е поврзана со зголемен ризик од појава на епилептиформни напади. Невротоксичноста на трамадолот најчесто се манифестира со епилептични напади.

Ключни зборови: трамадол, употреба/злоупотреба, епилептични напади.

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