Tramadol Induced Seizure: Report of 106 Patients

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Abstract

Background: Seizure is one of the possible adverse effects of tramadol hydrochloride, a synthetic, centrally-acting analgesic, prescribed for the treatment of moderate to severe pain. In this study, we describe 106 patients with tramadol induced seizures.

Methods: The patients, who were referred to Nemazee Hospital, Shiraz, Iran, from March 2006 to March 2008, were examined in this cross-sectional study. All of the patients had experienced seizure(s) after ingesting tramadol. Each patient was interviewed for demographic data, history of epilepsy, family history of epilepsy, duration of tramadol use, total dose and the last dose of ingested tramadol. Neurological examinations, routine laboratory tests, electroencephalography, and brain computed tomography were performed for each patient.

Results: One hundred and six patients were studied (102 males and 4 females, mean age: 26.7±6.9 years). Among them, 92 (86.8%) had new-onset provoked seizure(s) induced by tramadol and in 14 patients (13.2%), tramadol ingestion was considered as a precipitating factor in the setting of previously-known epilepsy. Tramadol was prescribed by the physicians for alleviation of pain in 20 patients (18.9%) and abused in the remainder (86 patients, 81.1%). The dose of ingested tramadol before the seizure(s) was 50 to 1500 mg.

Conclusion: Tramadol may provoke seizures in patients with epilepsy and also in previously healthy people even within the recommended dose ranges. Because most of the cases had occurred in young abusers, strategies to prevent tramadol addiction should be sought.

Keywords: Tramadol; Seizure; Abuse; Iran

Introduction

Tramadol hydrochloride is a synthetic, centrally-acting analgesic used both parenterally and orally for the treatment of moderate to severe pain. It has dual mechanism of action; weak agonistic effect at the μ-opioid receptor, as well as inhibition of monoamine (serotonin, norepinephrine) re-uptake.¹ Seizure inducing effect of tramadol, as an adverse-effect, is controversial. Some studies have revealed that tramadol can only provoke seizures if used in excessive doses in epileptic patients or in co-administration with other seizure inducing drugs.² while other studies have shown that tramadol may induce seizures even with the recommended doses and without any comediations.³⁴

In this study, we report 106 patients with tramadol induced seizure(s). Their epidemiological, clinical, electroencephalographic, and radiological findings are discussed comprehensively.

Materials and Methods

All patients who were referred to Nemazee Hospital, Shiraz, Iran, from March 2006 through March 2008, with seizure(s) after ingesting tramadol were studied after signing a consent form. The patients with known epilepsy, who had had seizure since one year before their admission, were excluded. In other words, non-epileptic patients and also patients with well-controlled epilepsy were included. All the patients

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had taken tramadol within 12 hours before their seizure. After taking medical history, physical examination, brain computed tomography (CT) and routine laboratory tests, all of the patients with primary and secondary brain tumors, substance withdrawal or overdose, central nervous system (CNS) infections, metabolic encephalopathy, hypertensive encephalopathy, head injury, pre-eclampsia and eclampsia, and any conditions other than tramadol intake were excluded.

Demographic data, history of epilepsy, family history of epilepsy, duration of tramadol use, the total dose and the last dose of ingested tramadol were inquired from the patients (at the time they were fully alert) or their relatives by a neurologist. Electroencephalography (EEG) and brain CT scan were performed for all of the patients.

Results

One hundred and six patients (102 males, 4 females) were studied. Mean age of the patients was 26.7± 6.9 years (95% CI: 25.4- 28.0). All the patients had developed witnessed generalized tonic-clonic seizure(s) within 12 hours of taking tramadol orally. Ninety two patients (86.8%) had new onset seizures, provoked by tramadol. Fourteen of them (13.2%) had a history of epilepsy, but their seizures were well-controlled and they did not have any seizure during one year before their evaluation. Tramadol ingestion was considered as a precipitating factor in this group. Five patients (4.7%) had a history of febrile seizure in their childhood and 8 patients (7.5%) had first degree relatives with epilepsy. Two patients (1.9%) had recurrent tramadol induced seizures.

The dose of ingested tramadol during a 12-hour period before seizures was 50 to 1500 mg (363.2 ± 303.1, 95% CI: 305.5-420.9). The duration of tramadol ingestion in the patients was in the range of 1 to 365 days (84.9 ± 63.7, 95% CI: 72.8-97.0). Tramadol had been prescribed by their physicians for pain alleviation in 20 patients (18.9%). Eighty six patients (81.1%) had abused the drug. The dose of ingested tramadol before seizure in the group taking it with prescription was 133.3±87.4, 95% CI: 116.7-149.9 (range 50-400 mg) and the mean duration of its ingestion was 3.4±2.4, 95% CI: 3.0-3.9 (range: 1-7 days). This dose in the group with tramadol abuse was 419.9±328.9 mg , 95% CI: 357.3-482.5 (range: 50 to 1500 mg) and the duration of its ingestion was 105.1±87.4 days (95% CI: 88.5-121.7, range: 3 to 365 days). Eighty five patients (80.2%) developed seizure with a daily dose equal to or less than 400 mg (maximal recommended daily dose: 400 mg). Twenty one patients (19.8%) developed seizure with doses above 400 mg.

Many patients who abused tramadol had also a history of abuse of other drugs including antidepressants (five patients, 5.8% abusing group), alcohol (5 patients, 5.8%), and opiates (20 patients, 23.3%). However, it should be mentioned that all ictal events that could be considered as withdrawal or overdose of these or other drugs were meticulously excluded through history taking. We followed all the patients for 5-15 months and 3 (2.8 %) of them had recurrent seizures due to recurrent tramadol intake.

Postictal EEG, which was conducted 1-3 days after the seizure event, was normal in 50 patients (47.2%). It also showed non-specific findings, including diffused slowing in 49 patients (46.1%) and epileptiform discharges in seven patients (6.6%). Of the patients with abnormal EEG with epileptiform discharges, four had previously-known epilepsy and three were patients with the first seizure, provoked by tramadol. All the patients had normal brain CT scans.

Discussion

In this study, we reported a series of 106 patients with tramadol induced seizure(s). It is well-known that tramadol may induce seizures in large doses.\(^1\)\(^,\)\(^6\) In one study, it was observed that neurotoxicity of tramadol commonly manifests as generalized tonic-clonic seizures occurring most frequently within 24 hours after tramadol intake. Seizures were more common in younger abusers with a longer duration of exposure to tramadol and with the combined use of tramadol with alcohol.\(^5\) Some other studies have revealed a relatively low risk of seizures with tramadol, unless it was taken by patients with epilepsy or taken with other seizure inducing drugs.\(^2\)\(^,\)\(^4\) while others have shown seizure-inducing effects of tramadol even in therapeutic levels.\(^5\)\(^,\)\(^9\) Interestingly, one animal study has considered an anti-epileptic activity for tramadol.\(^10\) In our patients, tramadol provoked seizures not only in supratherapeutic doses, but also in the recommended therapeutic doses even as low as 50 mg. As a matter of fact, more than 80% of our patients had seizure(s) after ingesting recommended doses of tramadol. This indicates that tramadol is a...
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potent seizure inducing agent and caution should be taken for its prescription.

In our study, seizures were provoked in less than 12 hours after ingesting 50 to 1500 mg tramadol. In another study, seizures were commonly induced by tramadol immediately after its ingestion (in less than 24 hours); however, 16% of the patients presented with seizures after 24 hours of tramadol intoxication. In that study, 55% of the patients revealed multiple seizures, but in our study, just 2.8% of the patients had recurrent seizures. This difference could be due to different approaches to the patients. We strongly recommend that all patients should avoid using tramadol in the future. Male predominance and tonic-clonic nature of seizures were similar in this and other studies.\(^5\)

Although the current study is not a population based study, the high number of patients, who abused tramadol, suggests the probability of high prevalence of tramadol abuse in our community. It was initially proposed that tramadol had a low potential for abuse and dependence \(^1\) however, tramadol may produce high abuse potential,\(^12\) and it has been reported that tramadol overdose is one of the most frequent causes of drug poisoning in Iran, especially among young male adults, with a history of substance abuse and mental disorders.\(^1\)

One of the limitations of this study was our inability to measure the blood level of tramadol, which prevented us from drawing firm conclusions with regard to its temporal relation and even causality with seizures. We were also unable to measure other drug levels to exclude any comedinations and we had to rely on the taken history. However, the large number of the patients in our study and the consistency of our results with previous studies suggest that this potentially life threatening adverse reaction (seizure) of tramadol should be considered seriously at the time of its prescription or ingestion. Also, informing the general population, particularly the youth, of the probable consequences of tramadol ingestion is of paramount importance and strategies to reduce tramadol addiction should be sought.

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Conflict of interest: None declared.

References


6 http://en.wikipedia.org/wiki/Tramadol

7 http://www.medicinenet.com/tramadol/article.htm


