

Intravenous Tramadol-Induced Seizure: Two Case Reports

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ABSTRACT

There are a few reports of seizure induced by tramadol at therapeutic dose. Two case reports of repeated seizures with following agitation due to treatment with tramadol are presented here. Both of them have similar presentation and tramadol was injected intravenously at therapeutic doses. Tramadol prescription especially intravenously can evoke seizure with agitation or even status epilepticus. Tramadol should be cautiously prescribed especially for patients with history of epilepsy, addiction and old ages.

Keywords: *Tramadol, Seizure*

Tramadol is a new synthetic, centrally acting analgesic agent. The mechanism of action of tramadol has yet to be fully elucidated, but it is believed to work through modulation of the gamma-aminobutyric acid (GABA)-ergic, noradrenergic and serotonergic systems. Tramadol, and its metabolite, known as M1, have been found to bind to μ -opioid receptors thus exerting their effect on GABAergic transmission, and to inhibit reuptake of 5-hydroxytryptamine (5-HT) and *noradrenaline*. The second mechanism is believed to be important since the analgesic effects of tramadol are not fully antagonized by the μ -opioid receptor antagonist *naloxone* [1].

Tramadol is an option for the treatment of rheumatologic pain. Its mode of action and safety profile distinguishes it from other opioids. Tramadol differs from other opioids by combining a weak opioid and a monoaminergic mode of action. It is effective in different types of moderate to severe pain, including neuropathic pain. Moreover, as the mode of action of tramadol does not overlap with that of non-steroidal anti-inflammatory drugs (NSAIDs), it is a useful agent to be combined with these drugs. Tramadol induces fewer opioid adverse reactions for a given level of analgesia compared with traditional opioids [2].

There is still controversial data about pro- or anti-convulsant effect of tramadol *in vitro*, some researches demonstrated that tramadol has anticonvulsant effect in mice but there are many report of tramadol-induced seizure in humans [3]. Seizures have been reported in patients receiving the drug in overdose and, rarely, at the recommended dose unless it is taken by people with

epilepsy or taken with other drugs that reduce the seizure threshold [4].

The smallest amount of tramadol associated with seizure was 200 mg, and 84.6% of seizures occurred within 6 hours administration. In a general population, there is association between seizures and tramadol use in males, long-term therapy, suicide attempts, intentional abuse or misuse, and tachycardia [5].

Dose adjustment is only necessary in patients over 75 years of age, or in those with either hepatic or renal insufficiency. Tramadol should be avoided or used with caution in epileptics, or in individuals who are receiving seizure-threshold lowering drugs [6].

There are a few tramadol-induced seizure reports around the world and this is the first report in Iran.

REPORT OF TWO CASES

The first case was a 21 years old girl who was referred to emergency ward with repeated seizures. According to history, she had a headache since the day before and due to medical prescription, she received intravenous injection of tramadol 100 mg slowly. During infusion, seizure occurred and because of repeated and uncontrolled seizures she was referred here. No significant past medical history was noted, there was no family history for epilepsy and patient had no history of seizure or head trauma. She didn't receive any other medication except tramadol. The patient was in postictal state. There was no fever, pupils had normal light reaction and there was no anisocoria. Fundoscopy was normal. Brain imaging including CT-Scan and MRI were

normal. CSF examination showed no abnormality. After anticonvulsant therapy and controlling seizure with improving awareness of patient she found severe agitation with hallucination. Behavior abnormality was controlled with antipsychotic medication. After 24 hours she got better, there was no more seizure. The patient was fully oriented and awake, and there was no hallucination. EEG was normal. She was discharged and after 9 month follow up there was no new seizure.

The second case was an 18 years old boy for whom tramadol had been prescribed because of headache. He had received tramadol 100 mg intravenously which caused seizure just after injection. He was referred for repeated attack of seizures and then he had a severe agitation with aggressive behavior and visual hallucination, he had no fever on admission. He was awake but confused and disoriented. Other neurological exams were normal, blood sugar and serum electrolytes were normal. Brain imaging, EEG and CSF examination were also within normal limits. About 48 hours after controlling seizure and appropriate antipsychotic therapy the patient got better and about 3 days later he was discharged. There was no new seizure during 6 month follow up.

COMMENT

It is important to consider tramadol as a possible cause of seizures, especially in overdose administration [7]. As Labate and Newton mentioned in their study, the seizures were generalized tonic-clonic, without auras or focal features. In their study no patient had a prior history of seizures, and none had a recurrence since they had ceased taking tramadol [8].

On the other hand some authors like Jick et al believe that there is no significantly increased risk of seizure among patients who take tramadol. They found no increased risk of idiopathic seizures associated with exposure to tramadol alone. So they concluded that seizures seemed rarely attributable to the agent [9]. Gass et al also suggested that the risk of idiopathic seizures was similarly elevated in each analgesic exposure category compared with nonusers, suggesting that the risk for patients taking tramadol was not increased compared with other analgesics [1].

The data demonstrate that kindling enhances the susceptibility of rats to convulsant adverse effects of tramadol and its enantiomers, indicating that a preexisting lowered seizure threshold increases the risk of tramadol-induced seizures [10].

Much of the toxicity in tramadol overdose appears to be attributable to the monoamine uptake inhibition rather than its opioid effects. Agitation, tachycardia, confusion and hypertension suggest a possible mild serotonin syndrome. The serotonergic modulating properties of tramadol mean that it has the potential to interact with other serotonergic agents. There is an increased risk of **serotonin syndrome** when tramadol is taken in combination with reuptake inhibitors (e.g. selective Serotonin reuptake inhibitor-SSRIs), agents that potentiate the effect of 5-HT (e.g., monoamine oxidase inhibitor-MAOIs), or 5-HT agonists [11].

Apparently according to these cases and also previous reports tramadol can induce seizure in therapeutic range and even status epilepticus may occur. Something that could be noticed is that this epileptogenicity is especially increased in intravenous prescription and also association of seizure with agitation could be considered due to serotonergic effect as mentioned before.

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