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CLINICAL VIGNETTE

Did the Pain Medication Cause My Seizures? A Case of Tramadol-Induced Seizure Activity

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Case report

A 93-year-old male with coronary artery disease, complicated by a cardiac arrest, diabetes mellitus, depression, and osteoarthritis was hospitalized for new onset tonic clonic seizures. This was his first episode and included right arm and head eversion, loss of consciousness, and post-ictal state. The seizure lasted approximately five minutes. The patient's medications include aspirin, clopidogrel, carvedilol, lisinopril and atorvastatin for coronary disease; glargine and lispro insulin for diabetes; lexapro for depression; and more recently tramadol for knee and leg pain. The patient underwent a thorough neurologic exam and evaluation by neurology. MRI and EEG were both unremarkable. It was later concluded that the seizures were most likely provoked by tramadol exposure. This case illustrates an interesting example of seizure activity precipitated by tramadol use.

Discussion

Tramadol is a centrally acting opioid like analgesic that has two synergistic mechanisms of actions. It has serotonin reuptake inhibition and acts as a weak opioid agonist and as a monoamine neurotransmitter reuptake inhibitor. It is extensively metabolized by the liver and 30% of the parent drug and 60% of active metabolites are excreted in the urine.¹

Tramadol has been generally well tolerated in clinical trials. Unlike other opioids, tramadol has little effects on the respiratory or cardiovascular function. It can be a reasonable option for the elderly, for patients with impaired renal or hepatic function, and for those where non-steroidal anti-inflammatory drugs are contraindicated. Tramadol is a generally well tolerated analgesic option with lower likelihood for dependence compared to other narcotics. A rare but important side effect is seizures, especially in patients taking medications that lower the seizure threshold, like selective serotonin reuptake inhibitors (SSRI). In addition, tramadol may precipitate serotonin syndrome (a potentially life-threatening drug-interaction manifested by excess serotonin effect resulting in cognitive, autonomic and somatic effects) in patients taking SSRI.^{2,3}

There are conflicting reports on the incidence of tramadol and seizure activity. One study looked at 215 tramadol users during a 5-month period to assess the incidence of seizure activity.⁴ For those identified with seizures, EEG and CT scan of the brain

were done. Also mean dose of tramadol was used to compare between patients with and without seizures. The majority of those with seizures were male and the seizures were categorized as generalized tonic-clonic. Also, there was no statistically significant difference in dose of tramadol used and the incidence of seizures.⁴

Seizures due to tramadol may occur in both therapeutic and supra-therapeutic dose ranges. One study indicated that the majority of patients had seizures after ingesting doses of tramadol as low as 50mg.⁵ Another study evaluated a cohort of adults who used tramadol. Although less than 1 percent had a reported seizure, the risk of seizure increased 2-6 fold when other drugs and comorbidities were included. The risk increased in those with a history of alcohol abuse, stroke or prior head injury, and in those on other anti-depressants and anti-psychotic medications that can lower the seizure threshold.⁶ Similarly, seizures were more common in males and EEG findings did not always indicate abnormal epileptiform activity. An Australian study in a seizure clinic found tramadol accounted for 8.2 percent of new onset seizures and was the drug considered to most commonly provoke seizures when compared to other opioids.⁷ However, one study found no increased risk of seizures with tramadol use,⁸ and another concluded that there was no higher risk compared to other analgesic monotherapies.⁹

Conclusion

Tramadol is a synthetic opioid analgesic that also inhibits serotonin and noradrenaline reuptake. It is a commonly used analgesic and is felt to have a better tolerated side effect profile than other more potent opioids. It can help with both nociceptive and neuropathic pain and generally is less sedating and has less effect on respiratory depression. However, a rare but notable side effect includes seizures that have been reported in patients receiving this drug. The incidence of seizures may not necessarily be dose dependent and seizures can occur in both therapeutic dose and overdose ranges.

Tramadol has the potential to increase the risk of seizures, especially if used in patients with a history of epilepsy, prior stroke or head injury, or if used in conjunction with other medications that can lower the seizure threshold such as anti-depressants. In this case, the patient did not have a history of

epilepsy or stroke, but was on an anti-depressant escitalopram when the tramadol was started. Such combination may have lowered the seizure threshold and increased his risk of seizure onset. This is a very rare occurrence. Thus, such adverse effects of tramadol should be considered carefully when prescribing new therapy. Patients on this agent should be monitored closely especially if they have higher risk comorbidities or are on concomitant psychiatric medications.

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