Mechanisms of tramadol intoxication

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Core tip: Tramadol is an old analgesic with controversial influences. This drug has effects on multiple receptor systems including serotonin and norepinephrine, mu-opioid, gamma amino butyric acid and histamine receptors.

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Tramadol has a potent antidepressant effect. The risk of poisonings and deaths attributed to tramadol rises due to expanding of deleterious behaviors opioids and analgesics use. Abuse of this drug, alone and in combination with other substances, induced toxicity which several studies proved it biochemically and histopathologically in various organs (1,2).

This drug is responsible for life-threatening poisonings resulting in central respiratory depression, seizure, impairment of consciousness, agitation and manifestation of serotonin syndrome (2). Tramadol has an anti-nociceptive activity mediated by μ-opioid receptors, serotonin and norepinephrine re-uptake inhibition (1). Tramadol induces serotoninergic effects in transverse hippocampal slices (3). Tramadol inhibits mono-amine re-uptake. It decreases serotonin catabolism. However, it is not a serotonin releaser. Hence, serotonin may increase in the brain (3,4). It decreases catabolism and turnover of dopamine and stimulates the dopamine receptors. Dose-dependent norepinephrine and serotonin reuptake inhibitions are well established (3).

According to a recent study, seizure thresholds were negatively correlated with serotonin levels and intracerebroventricular methysergide that is a nonselective serotonin receptor antagonist lowered the tramadol-related seizure threshold (3). In addition, mydriasis and tachycardia, signs of the serotonin syndrome, were significantly related to a higher risk for seizure. In controversy, some researchers highlighted that tramadol-induced seizures are not only dependent on brain serotonin (6,7).

Importantly, tramadol increases concentrations of norepinephrine in brain. Tachycardia and mild hypertension may manifest with noradrenergic effects (1,3).

The previous studies suggested that multiple alternative receptor systems such as histaminergic, dopaminergic, opioid, and gamma amino butyric acid neurotransmission have been involved in triggering tramadol-induced seizures (3,6,7). In controversy, histamine1 receptor activation-linked pathway that modulates the release of histamine from mast cells has been proposed to potentiate seizures in tramadol toxicity (7) while anti-histaminergic activity has been known to potentiate seizures. Additionally, a survey found that hypothalamic histamine concentrations remained unchanged after tramadol administration. Tramadol-induced early-onset may increase in brain concentrations of serotonin. Also norepinephrine was not altered by the diazepam with tramadol combination (3). It has been demonstrated that opioid receptor over-activation can induce seizures related to inhibition of the gamma amino butyric acid receptors, hence tramadol inhibits the gamma amino butyric acid release in a central nervous system (6).

Tramadol metabolism by cytochromes P450 3A4, 2D6 and 2B6 produces four metabolites that one of them has approximately 200 times higher affinity to mu-opioid receptors in comparison to tramadol. In addition, cytochrome P450 2D6 (CYP2D6) is an enzyme that is expressed in the liver and substantia nigra. It is encoded by the CYP2D6 gene and exhibits wide polymorphism leading to variation in toxic and therapeutic effects of tramadol (1).

The previous studies proved that tramadol can impair memory when using acutely or chronically, while the destruction of serotonergic afferents to the hippocampus

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has not effects on spatial memory. Oxidative stress had an important role in the memory impairment. Tramadol abuse causes a significant elevation in lipid peroxidation with reduction in the antioxidant activity. Thus, oxidative stress might be one of the mechanisms of memory impairment of this drug (1,4,5).

Some people use tramadol to increase their sexual propensity or improvement of their sexual function. Once a person develops dependency to the drug, stopping of tramadol may lead to withdrawal symptoms. Tramadol withdrawal reactions are agitation, restlessness, anxiety, tremor, paresthesia, sweating, insomnia, hyperkinesia, and gastrointestinal symptoms. It should be noted that tramadol affects serotonin and catecholamines as well as µ receptors. Some of these symptoms may not completely related to opioids, while they are similar to serotonin and epinephrine reuptake blockers withdrawal symptoms (8). Sometimes tramadol is abused with other drugs as methadone, benzodiazepines and cyclic antidepressants, thus unusual symptoms may develop like pulmonary edema (9).

The exact mechanism of tramadol is not known yet. Thus, investigation of various receptors and mediators interacted in tramadol intoxication is necessary.

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