

Tramadol Pill Alone May Cause Serotonin Syndrome

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To the Editor: Tramadol is a synthetic opioid analgesic chemically related to codeine and is classified as a Class II drug for the treatment of moderate intensity pain according to the WHO recommendation. Tramadol has low affinity for μ - and κ -opioid receptors and inhibits the reuptake of both norepinephrine and serotonin (5-hydroxytryptamine) neurotransmitters. It stimulates the dopamine (D2) receptors and also inhibits the gamma amino butyric acid release in central nervous system.^[1] Serotonin syndrome (SS) is a potentially life-threatening adverse drug reaction to serotonergic medication. It can be produced by any drug or, more commonly, by a combination of drugs that increase central serotonin neurotransmission. Tramadol is reported primarily in the psychiatric literature as causing SS in combination with selective serotonin reuptake inhibitors (SSRIs) and atypical antipsychotics.^[2] High doses of tramadol may also induce SS. SSRIs can inhibit the CYP2D6 isoenzyme metabolism, resulting in therapeutic overdose of tramadol and inducing SS in susceptible individuals. We reported a rare case of typical clinical presentation of SS occurred just after taking two tramadol pills.

A 23-year-old man came to the emergency room on July 25, 2015, with the chief complaint of generalized muscular spasm with periodic sudden limb movements, mostly in the lower limbs. There were no any history of diseases and taking medications. He was not having a seizure. Four hours before admission, he took a tablet of tramadol, 200 mg orally to prevent premature ejaculation. He complained of muscular and back pain and abdominal cramps. Upon examination, he was irritable and restless but he had answered the questions completely. The vital signs were as follows: heart rate 110 beats/min, blood pressure (BP) 90/60 mmHg, respiratory rate 25/min, and body temperature 38.9°C. Pain in deep palpation of preumbilical area was found in the physical exam. In the neurological exam, tremor and generalized weakness were obvious and he was not able to sit. In addition, hyperreflexia mainly in the ankles and periodic myoclonus triggered by touching were visible. No focal neurological signs were found. Primary lab results were as follows: serum Na 143 mmol/L, serum K 4.5 mmol/L, white blood cell $19.2 \times 10^{12}/L$, Hgb 143 g/L, platelet 164,000/ μ L, serum creatinine (Cr) 0.012 g/L, blood urea nitrogen (BUN) 0.62 g/L, creatine phosphokinase (CPK) 2300 U/L, alanine aminotransferase 180 U/L, aspartate aminotransferase

265 U/L, pH 7.28, HCO_3^- 15 mmol/L, and PCO_2 29 mmHg. Chest X-ray and head computed tomography scan were normal. The result of cerebrospinal fluid was also normal. A central venous catheter was inserted and normal saline of 500 ml/h was given. After a few hours, BP and urinary output of the patient improved; however, tachycardia was still present. To reduce his symptoms, intravenous benzodiazepine was administered. After 2 days, he recovered from rhabdomyolysis and renal dysfunction. He was discharged home on the 3rd day.

Currently, the most common cause of poisoning in Iran is drug poisoning, and almost 25,000 people passed away just in Tehran because of drug and chemical poisonings. Among these, 12,000 patients were hospitalized and 1200 of them were transferred to intensive care units.^[3] Tramadol poisoning is one of the most common causes of poisoning in Iran, and tramadol abuse and overdose have also increased in Iran recently.^[3] Therapeutic dose of tramadol is usually 50 mg orally, or 100 mg via injection, or 400 mg/d rectally.^[2] Medical usage of tramadol has been legally allowed since 1995 in the United States and 2003 in Iran. Seizure and apnea are the most important life-threatening clinical adverse events of toxic dose or even therapeutic dose of tramadol. There are no specific diagnostic tests for SS; therefore, a complete and accurate medical and drug history is mandatory for diagnosis, which is made based on Hunter Serotonin Toxicology or Steinbach's Criteria. In most cases, SS is caused by co-administration of medications such as using tramadol with an SSRI, tramadol with a tricyclic antidepressant (TCA), a TCA with an SSRI, or an SSRI with another antidepressant.^[4] Many people tolerate these co-administrations, and SS occurs when dosage of one or two of these medications is increased. Mechanism of this syndrome is metabolism of tramadol in liver by hydroxylation and conjugation with glucuronide which leads to metabolism of SSRI via competitive inhibition. In this patient,

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Received: 14-10-2015 **Edited by:** Xiu-Yuan Hao and Xin Chen
How to cite this article: Aminiahdashti H, Shafiee S, Mousavi SJ, Hajiaghaei G. Tramadol Pill Alone May Cause Serotonin Syndrome. Chin Med J 2016;129:877-8.

Access this article online

Quick Response Code:



Website:
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DOI:
10.4103/0366-6999.178957

we observed that tramadol can individually cause SS (including restlessness, autonomic disorders, and neurological symptoms). Moreover, patient had rhabdomyolysis, renal dysfunction, and elevated liver enzymes. Rhabdomyolysis with elevation of CPK has been mentioned as a rare but serious complication of tramadol poisoning; however, recurrent seizures and prolonged immobility are considered to be caused by CPK level elevation and rhabdomyolysis.^[5] In chronic tramadol users, elevation of liver enzymes, BUN, and Cr was also found. The symptoms of this patient were not consistent with opioid poisoning (myosis and respiratory depression). Although the symptoms were similar to benzodiazepine withdrawal symptoms (muscular twitch and changes in vital signs), there was no drug history of taking benzodiazepines for this patient. Many physicians are familiar with antidepressant-induced SS but not with SS induced by analgesic drugs such as tramadol. Therefore, it is crucial for physicians to be aware of undesirable serotonergic adverse effects of tramadol.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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