ToxTidbits

Maryland Poison Center
UNIVERSITY OF MARYLAND SCHOOL OF PHARMACY

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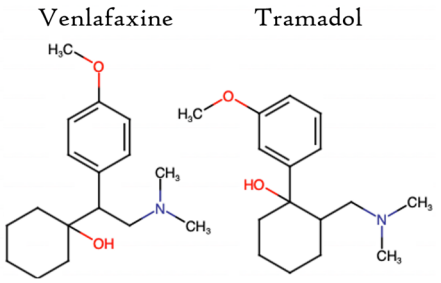
The Maryland Poison Center's Monthly Update: News, Advances, Information

Tramadol revisited



Tramadol was first available in the United States in March 1995 and assigned as a schedule IV substance in 2014. Tramadol is not a strong opioid agonist (~6000x weaker than morphine), but its metabolite, *o*-desmethyltramadol, has a much higher affinity for the μ-opioid receptor (*Clin Pharmacokinet* 2004;43 (13):879-923). The caveat is that *o*-desmethyltramadol is formed through metabolism by cytochrome P450 2D6 (CYP 2D6) which is known to have varying activity based on genetic polymorphisms. Caucasians and individuals from the Middle East and Indian subcontinent are more commonly rapid or ultra-rapid CYP 2D6 metabolizers compared to Asian populations and will generate more of the opioid metabolite (*Toxicol Envir Health* 12(5-6), 334-61). Although the parent compound is not an opioid, tramadol shares structural similarities with venlafaxine, and therefore inhibits serotonin and norepinephrine reuptake (SNRI). To quote one toxicologist's thoughts on its mechanism is probably the best way to understand it: it is like giving a patient venlafaxine and morphine in an unknown ratio.

This leads us to the clinical effects that we see in the overdose setting. As *o*-desmethyltramadol functions as an opioid, overdoses may present with miotic pupils, respiratory depression, and central nervous system depression. However, due to the parent compound's SNRI effects, patients can manifest signs and symptoms of serotonin toxicity including tachycardia, agitation, clonus, diaphoresis, and hypertension. This is especially important in patients who are on other serotonergic agents. Additionally, seizures are common in overdoses with frequency usually in the 10–15% range, but in some studies as high as 50–60% (*Arch Acad Emerg Med*. 2020 May 17;8(1):e59; *Clin Toxicol* 57.8 (2019): 692-6). The smallest dose of tramadol that resulted in a seizure was 200 mg in a 26-year-old male with no history of epilepsy, and 85% of patients who experienced seizures did so within 6 hours of the overdose (*Ann Pharmacother*. 2005 Jun;39(6):1039-44). Another unique effect of tramadol is hypoglycemia which can occur with therapeutic use, seems to be dose related, and those with diabetes, renal insufficiency, and older age appear to be at higher risk (*Ann Pharmacother*. 2020 Mar;54(3):247-53).

Treatment for tramadol overdoses is primarily supportive and dependent on the presenting symptoms. Gastrointestinal decontamination with activated charcoal within 1-2 hours is recommended as opioid effects may delay gastric emptying. If the patient has an opioid toxidrome, treatment with naloxone is indicated. For agitation, tremulousness, and/or seizures, benzodiazepines are the first line therapy. Although there are conflicting reports on naloxone to treat seizures or naloxone causing seizures after tramadol ingestion, it is important to remember that mechanistically, naloxone does not have any antiepileptic properties. The likelihood of patients seizing with tramadol is unrelated to the administration of naloxone and should not preclude naloxone use (*Int J Prev Med*. 2019 Oct 9;10:183).

Tramadol is a unique medication whose effects depend on individual metabolism which are hard to predict. Patients can present with an opioid toxidrome, serotonergic toxicity, along with seizures. Treatment is largely supportive with naloxone, benzodiazepines, and airway management.

Did you know?

Tramadol is associated with QTc prolongation.

In a study assessing EKGs 3-5 days after tramadol initiation at 150 – 400 mg/day, QTc's were 22-26 msec longer depending on the calculation formula with high correlation to plasma concentrations. Additionally, renal failure was a risk factor for a higher concentration and QTc prolongation (*Curr Drug Saf*. 2016;11(3):206-14). Another study found other common EKG abnormalities in patients with tramadol overdose: sinus tachycardia, a deep S wave in leads I and aVL, and right axis deviation. Notably sinus bradycardia or a Brugada pattern were rare findings (*Emerg (Tehran)*. Summer 2016;4(3):151 -4).

Faisal Syed Minhaj, PharmD
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