Tapentadol-Induced Seizure in a Patient With Opioid Dependence

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Tapentadol is a centrally acting "atypical" opioid analgesic with dual mechanism wherein it acts as a μ-opioid receptor agonist and inhibits norepinephrine reuptake.[1,2] Due to its easy availability and cheap price, tapentadol is rapidly gaining infamy among drug users.[3,4]

Opioids result in neuroexcitation, which can cause nystagmus, extremity flexion, rigidity, myoclonus, and seizures.[5] While most of the commonly used opioids have shown dose-related seizure activity in mice as well as human subjects at sufficiently high doses,[6] no seizure activity following tapentadol use has been reported in any phase of international clinical trials.[7] Here, we present a case of tapentadol-induced seizure in an opioid abuser.

Case Report

A 25-year-old man presented to the treatment center with opioid intake for 8 years and 3 seizure episodes in the last 24 hours. He initiated opioids out of curiosity, initially as opium (natural opioid) and codeine. For the last 4 years, he had been using 1.5 g of heroin daily. In 2020, he was initiated on tapentadol as a part of opioid detoxification, but he dropped out and returned to his previous pattern. As tapentadol had effects similar to heroin, he continued taking 100–200 mg occasionally to partially overcome the withdrawal symptoms. Once to accentuate his experience, he took his average dose of heroin (1.5 g) and supplemented with 300 mg of tapentadol. He did experience an intense high, but also had multiple seizure episodes over the next 4 hours. The seizure episodes took place approximately 1 hour, 3 hours, and 3 hours and 30 minutes after the tapentadol intake. Each episode was characterized by increased tonicity of all 4 limbs of the body and frothing from the mouth, with tongue bite, up rolling of the eyeballs, and unconsciousness for a period of 5 minutes and no recall of events that occurred during the episode after gaining consciousness. Over the past 6 months, 4 seizure events had been reported under similar circumstances, the last episode being 2 days before his presentation to our center. The patient did not report changing his source of drug procurement or any significant changes in his daily heroin intake over this period. He did report smoking cannabis and cigarettes regularly for the last year.

In the past, he exhibited frequent disobedience and truancy but had no history of head injury, fever with neck rigidity, or seizure disorders. His general physical, systemic, and mental status examination results were essentially normal. His blood biochemistry (complete hemogram, liver and kidney function tests, serum electrolytes, viral markers), magnetic resonance imaging, and electroencephalogram revealed no abnormality. Consultation with the neurology department elicited no definitive causes for the seizure episodes. No family history of seizure disorder was reported.

He was detoxified using 2 mg of tablet buprenorphine, which was subsequently tapered to 0.8 mg/d over the next week. He was discharged and maintained well on buprenorphine 0.8 mg for 12 weeks with no further seizure episodes before dropping out due to COVID-19–related lockdown.

Discussion

We report a case, perhaps the first in the literature, associated with tapentadol-induced seizures. Since its approval for chronic pain approximately a decade ago, tapentadol has been classified as a relatively safe opioid analgesic with mild adverse recations.[7,8] Drugs with opioid activity at higher doses can cause convulsions, especially tramadol and dextropropoxyphene.[6] Different mechanisms have been postulated for this activity including (1) changes in central catecholamine concentrations in the dopaminergic pathways and (2) increase in release of excitatory neurotransmitters.[9] Further, tramadol causes inhibition of γ-aminobutyric acid-A receptors and inhibits the reuptake of norepinephrine and serotonin neurotransmitters, reducing the seizure threshold.[10,11] Despite having similarity with tramadol, tapentadol is not usually associated with convulsions.[12]

Since our patient was using a combination of heroin and tapentadol, it may be assumed that resulting opioid toxicity could have led to seizures. However, higher intake of heroin (2–2.5 g) on multiple occasions in the past did not result in any complications, and it was only with the addition of tapentadol that convulsions were reported. Thus, it is very likely that additional actions of tapentadol led to convulsions, rather than opioid toxicity. A score of

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5 was obtained on the Naranjo Adverse Drug Reaction Scale,[13] suggesting tapentadol was the probable cause for these convulsions and further supporting our assumption. Animal studies[14] have shown that tapentadol at higher doses can produce convulsions. In addition, recent updates in tapentadol product information have included a warning on combining it with seizure threshold–lowering drugs.[15]

Our case highlights that tapentadol can cause convulsions when combined with other opioids, especially in susceptible individuals. This has implications for clinicians who might prescribe tapentadol for chronic pain or opioid detoxification when opioid substitution treatment is unavailable. Further, there are implications for people with opioid dependence as well given that they are likely to use tapentadol as a replacement or to enhance the effect of opioids and may develop convulsions.

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REFERENCES

1. Ventura L, Carvalho F, Dinis-Oliveira RJ. Opioids in the frame of new psychoactive substances network: a complex pharmacological and toxicological issue. *Curr Mol Pharmacol*. 2018;11(2):97–108.
2. Schröder W, Vry JD, Tzschentke TM, et al. Differential contribution of opioid and noradrenergic mechanisms of tapentadol in rat models of nociceptive and neuropathic pain. *Eur J Pain*. 2010;14(8):814–821.
3. International Federation of Pharmaceutical Manufacturers & Associations (IFPMA). 2014. Comments to the World Health Organization (WHO; Expert Committee on Drug Dependence), Tapentadol Critical Review Report. IFPMA website. Accessed May 19, 2021. https://1drv.ms/b/s!ApKWQTZMM8GvwVKUFo-gf3Q2wWXJ?e=UhinJV
4. Mukherjee D, Shukla L, Saha P, et al. Tapentadol abuse and dependence in India. *Asian J Psychiatr*. 2020;49:101978.
5. Bailey PL. Stanley 17-1. Intravenous Opioid Anesthetics. In: Miller RD, ed. *Anesthesia*. 4th ed. New York: Churchill Livingston Inc; 1994:4.
6. Raffa RB, Stone DJ Jr. Unexceptional seizure potential of tramadol or its enantiomers or metabolites in mice. *J Pharmacol Exp Ther*. 2008;325(2):500–506.
7. Stollenwerk A, Sohns M, Heisig F, et al. Review of post-marketing safety data on tapentadol, a centrally acting analgesic. *Adv Ther*. 2018;35(1):12–30.
8. Vadivelu N, Timchenko A, Huang Y, et al. Tapentadol extended release for treatment of chronic pain: a review. *J Pain Res*. 2011;4:211–218.
9. Kofke WA, Garman RH, Tom WC, et al. Alfentanil-induced hypermetabolism, seizure, and histopathology in rat brain. *Anesth Analg*. 1992;75(6):953–964.
10. Hara K, Minami K, Sata T. The effects of tramadol and its metabolite on glycine, gamma-aminobutyric acidA, and *N*-methyl-D-aspartate receptors expressed in Xenopus oocytes. *Anesth Analg*. 2005;100(5):1400–1405.
11. Nakamura A, Narita M, Miyoshi K, et al. Changes in the rewarding effects induced by tramadol and its active metabolite M1 after sciatic nerve injury in mice. *Psychopharmacology (Berl)*. 2008;200(3):307–316.
12. Tsutaoka BT, Ho RY, Fung SM, et al. Comparative toxicity of tapentadol and tramadol utilizing data reported to the National Poison Data System. *Ann Pharmacother*. 2015;49(12):1311–1316.
13. Naranjo CA, Busto U, Sellers EM, et al. A method for estimating the probability of adverse drug reactions. *Clin Pharmacol Ther*. 1981;30(2):239–245.
14. Tschentke TM, De Vry J, Terlinden R, et al. Tapentadol hydrochloride. *Drugs Future*. 2006;31(12):1053–1061.
15. Medicines and Healthcare products Regulatory Agency (UK). Tapentadol (Palexia): risk of seizures and reports of serotonin syndrome when co-administered with other medicines. Drug Safety Update 12: 2-3, No. 6, Jan 2019. Publishing service.gov uk website. Accessed May 19, 2021. https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/770006/PDF-Jan-2019-publication.pdf