Tramadol induced seizure. *Is Isoniazid the culprit?*

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Tramadol is currently one of the most popular analgesic drugs for effective treatment of moderate to severe pain. Comparison with the traditional opioids is unfavorable regarding its seizure potential and hence; tramadol-related seizure is rarely observed. Herein, we report tramadol-induced seizure, possibly potentiated by isoniazid in a patient with Pott's spine with para-spinal abscess on anti-tuberculous treatment (ATT).

A 10-year-old girl, weighing 24 kg, suffering from Pott's spine with para-spinal abscess (T11-T12 level) on ATT (isoniazid 150 mg, rifampicin 300 mg, ethambutol 400 mg, and pyrazinamide 600 mg) for the last 2 months was posted for abscess drainage. She had significant sleep deprivation due to persistent back pain and inability to lie down in the supine position. Blood counts, renal, and liver function tests were within normal limits. After setting the IV infusion, oxygen was started under pulse oximetry to maintain 100% oxygenation. Pre-medication included 50 mg (2 mg kg^{-1}) tramadol (slow IV injection) for preemptive analgesia, and 2 mg (0.1 mg kg^{-1}) ondansetron IV, followed by 0.5 mg (0.05 mg/kg) midazolam IV. Immediately after the injection, she developed generalized tonic clonic convulsions with rolling up of the eyeballs and jerky movements of both upper and lower limbs. Diazepam 5 mg IV was administered immediately. Abnormal movements were terminated within 90 seconds. The pulse oximeter continuously showed 100% oxygenation throughout the episode. Surgery was deferred, and she was shifted to the ICU for close monitoring. She regained consciousness within 15-20 minutes with a Glasgow Coma Score of 14/15. There was no post-ictal confusion or weakness. There was no neck rigidity, and Kerning's and Brudzinski signs were negative. She was afebrile. An EEG showed normal fast frequency variant, with no abnormal findings. Serum electrolytes, blood sugar, and arterial blood gas analysis were within normal limits. Lumbar puncture was not carried out due to presence of adjacent para-spinal abscess. There was no recurrence of the seizure. Instead of open drainage, therapeutic aspiration was carried out under ultrasound guidance, and she was discharged from the hospital on conservative treatment without anti-epileptic drugs. She was seizure-free at one and 3 month follow up. Her guardian provided the written informed consent for publication of this report. The case was reported to the North Zonal Center of the National Pharmaco-vigilance Programme (NPP).

As she was unconscious, and the movements were generalized and there was a quick response to intravenous diazepam; it was clinically diagnosed as a generalized tonic clonic seizure. Whereas in a case of drug-induced dystonia, the patient is usually conscious, awake, and abnormal movements are localized and less likely to show such a prompt response to diazepam. A combination of more than 3 factors, namely, temporal relationship between the administration of tramadol and the occurrence of the seizure, presence of co-factors for seizure like isoniazid intake, sleep deprivation, pediatric age-group, no subsequent seizure episode on stopping the drug, and no history of seizures, supports the view that the event could be due to tramadol. The strength of association was examined using Naranjo's Adverse drug Reaction Probability Scale, in which a score of +6 was obtained suggesting a 'probable' link. The dose of midazolam used here was for sedation of the patient, and at this dose of 0.05 mg/kg, it does not show any anti-convulsive activity. The drug used to treat the convulsions was not midazolam, but diazepam, which is longer acting than midazolam and the dose is also 10 times more. However, the midazolam was given before the tramadol, but the tramadol might have initiated its action before the midazolam, as the tramadol has faster onset of action. So, it was inferred that the convulsions in the present case were not due to midazolam. There are a few isolated case reports of ondansetron induced seizures in the literature, but all of them with no causality assessment, multiple concomitant medications, and CNS metastasis. In 2000, Balakrishnan et al,[1] however, reported that ondansetron had potent anticonvulsant activity in rats. In view of our past extensive experience with ondansetron without any seizure episode, and its potent anticonvulsant action as reported by Balakrishnan et al,[1] we strongly feel that it is an unlikely causal agent in our patient.

The other causes of seizures in children, such as hypoxia, meningitis, encephalitis, electrolyte, and glucose abnormalities were ruled out by clinical examination and investigations. After carrying out a multicenteric prospective chart review and evaluation of 87 tramadol ingestions over an 11-month period, Spiller et al[2] concluded that seizures seen in these cases were brief, self-limiting, usually single events, and occurred within 4 hours of tramadol ingestion. We observed seizure in our patient immediately after tramadol injection, which raises the suspicion for the presence of another co-factor for seizure in light of the suggestion of Gardner et al.[3] Therefore, isoniazid, which the patient was taking as part of the ATT regimen was considered. Isoniazid has been known to induce or potentiate seizure like episodes, mostly because of overdose. Isoniazid may affect the sensitivity of the CNS to convulsive action of

co-administered drugs, like cefazolin and theophylline but in the literature, there was no report of probable interaction with tramadol. The strength of association using the 'Drug Interaction Probability Scale' obtained a score of +5, suggesting a 'probable' link.

The mechanism of tramadol-related seizure is still debatable; however, inhibition of the neuronal monoamine reuptake has been shown not to be a major mechanism.[4] Tramadol induced seizures from a probable interaction with isoniazid is biologically plausible. Isoniazid interferes with the phosphorylation of pyridoxine to pyridoxine phosphate. Pyridoxal phosphate is an active cofactor for the enzyme glutamic acid decarboxylase, which forms Gamma-aminobutyric acid (GABA). Isoniazid thus depletes GABA in the CNS and predisposes to seizures.[5] Morphine-like drugs have been reported to have excitatory effects, probably from inhibition of the release of GABA by interneurons in the hippocampal area. It is possible that, isoniazid may potentiate tramadol-induced seizures by a GABA modulating pathway. However, this hypothesis needs to be tested.

The present case report of isoniazid potentiating tramadol-induced seizure has huge implications in developing countries where a large population receive isoniazid-based anti-tuberculous drugs for tuberculosis, and where tramadol is also freely prescribed for various forms of the pain relief and pre-medication before induction of general anesthesia.

Received 1st October 2008. Accepted 31st December 2008.

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