Case Report

Intravenous tramadol induced simple partial seizures

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Abstract

Tramadol is a synthetic codeine analogue, used in the treatment of mild-to-moderate pain. Its well-known side effects include nausea, vomiting and dizziness. Seizures are a rare adverse effect of tramadol. Studies have demonstrated that tramadol can induce seizures and possibly exacerbate seizures in patients with predisposing factors, even at recommended dose. We herein report a case of acute pancreatitis with pseudocyst who presented with a brief episode of simple partial seizures on administration of single dose of tramadol 100 mg, intravenously.

Key Word: Tramadol, seizure

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INTRODUCTION

Tramadol isa synthetic codeine analogue, used in the treatment of mild-to-moderate pain. It has a dual mechanism of action. It is a weak mu opioid receptor agonist. Tramadol and its active metabolite, O-desmethyl tramadol, bind to μ opioid receptors and cause inhibition of ascending pain pathways.[1] Part of its analgesic effect is produced by the inhibition of uptake of norepinephrine and 5-hydroxy tryptamine (serotonin) and increased serotonin release which activates monoaminergic spinal inhibition of pain.[2] However, Tramadol is less effective for the treatment of severe or chronic pain. The peak plasma levels occur at about 1.5 hours after intake and plasma half-life is 5-6 hours. The duration of analgesia lasts for about 4-6 hours. Tramadol undergoes extensive metabolism in liver by a number of pathways, including CYP2D6 and CYP3A4, and also by conjugation, with subsequent renal excretion. The recommended adult dosage is 50-100 mg every 4 to 6 hours, not to exceed 400 mg/day[1,2] Side effects of tramadol include nausea, vomiting, dizziness, dry mouth, sedation, headache and mild respiratory depression. Seizures are a rare adverse effect of tramadol. Tramadol can cause seizures and possibly exacerbate seizures in patients with predisposing factors.[1] Tramadol-related seizures are short, tonic-clonic type of seizures that are self-limiting. This epileptogenic effect of tramadol occurs at both low and high doses.[3] Some studies demonstrated that tramadol induced seizures may also occur in therapeutic ranges, most frequently within 24 hours after tramadol intake-especially in subjects consuming other drugs such as alcohol, selective serotonin reuptake inhibitors, tricyclic antidepressants, and antipsychotics.[4]

CASE REPORT

A 35-year-old man was admitted with complaints of pain in the upper quadrants of abdomen since 16 days which was insidious in onset, pricking type, moderate-to-severe in intensity, gradually progressive and radiating to back. He also complained of on and off low-grade fever, vomiting and decreased appetite since 20 days. He had history of similar complaints twice in the last 2 months.

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There was no history of altered bowel habits or disturbed sleep. He was not an alcoholic or smoker and was not on any medication. There was no family history of epilepsy and patient had no history of seizure or head trauma in the past.On examination, he was conscious and oriented. His heart rate was 90 beats per minute and blood pressure was 116/78 mm Hg. Per abdomen examination revealed tenderness in the epigastric region and other systemic examination including central nervous system appeared normal. Patient was treated symptomatically with intravenous fluids (Normal saline), injection Vomiset (Ondansetron) 4 mg, tablet Paracetamol 650 mg and antibiotic, injection Taxim (Cefixime) 1 g was prescribed intravenously twice a day. Laboratory investigations revealed increased serum amylase (802.8 U/L) and lipase (311.9 U/L), increased total count (18,700 cells/mm^3), decreased haemoglobin (8.9 g/dl) and red blood cell count (3.18 million cells/mm^3) and normal liver function test. Ultrasonography and contrast enhanced computed tomography of abdomen showed features of acute pancreatitis with pseudocyst, in the anterior pancreatic region. Sincehe complained of severe pain on second day, which did not improve with NSAIDs, he was prescribed a dose of injection Tramadol 100 mg intravenously. Just after the injection he developed sudden, brief, jerky muscle contractions involving right upper extremity (right arm) and had difficulty in speaking. This single episode which was diagnosed as simple partial seizures lasted less than a minute and subsided without any medication. Patient was conscious during the episode. Tramadol was withheld without rechallenge and injection Pheniramine was administered intravenously. Dechallenge was positive. No such episodes were noticed further. After the episode, on examination, patient was conscious, alert and oriented. His vitals including heart rate (88beats/min), blood pressure (128/82 mm Hg) and respiratory rate (15/min) were with in normal limit. Computed tomography brain was normal.

DISCUSSION

Seizures have been reported in patients receiving Tramadol in overdose and, rarely, at the recommended dose unless it is taken by epileptic patients or those who are taking drugs that reduce the seizure threshold.[5] There are a few reports of seizure induced by tramadol at therapeutic dose. In 1998, Jick *et al.* found no increase in the risk of seizure upon use of tramadol alone,[6] while Gardner *et al.* found seizures in 1% of adults using tramadol, after the first tramadol prescription.[7] In both studies, patients received tramadol at therapeutic doses. They also found increased risk of seizure in patients in the age group of 25-54 years, those with more than four tramadol prescriptions and in those with a history of alcohol abuse, stroke or head injury. Rehni AK, *et al.* in his study suggested that tramadol exerts a seizurogenic effect on mice possibly via an opioid-dependent GABA inhibitory pathway.[8] Experimental studies have demonstrated that kindling enhances the susceptibility of rats to convulsant adverse effects of tramadol and its enantiomers, indicating that a pre-existing lowered seizure threshold increases the risk of tramadol-induced seizures.[9] Mehrpour Mreported two cases of intravenous tramadol-induced seizures and noticed that this epileptogenicity was especially increased with intravenous prescription and was associated with agitation, tachycardia, confusion and hypertension, suggesting a possible mild serotonin syndrome. In these two cases, early onset of seizure was seen (during intravenous infusion and immediately after intravenous injection of 100 mg of tramadol), as found in our case.[10] In the present case, paracetamol and ondansetron were co-administered with tramadol, which do not usually contribute to seizure. Appropriate investigations ruled out any organic cause of seizures and there was no apparent alternate cause other than intravenous tramadol that could have caused the seizure. Considering the temporal relationship and the fact that patient recovered after stopping the drug, the causality of the reported event is considered probable to Tramadol.In World Health Organization – Uppsala Monitoring Centre (WHO-UMC) causality system, this event can be considered under probable/likely category and on Naranjo Adverse Drug Reaction Probability Scale, the total score was 5 out of 13 which reflects the 'probable causal association'. Thus, we conclude that intravenous tramadol can induce seizures even in the recommended dose (100 mg), and hence it is important to monitor for adverse reactions vigilantly when tramadol of various dose ranges are administered.

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