

## Seizures after intravenous tramadol given as premedication

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### ABSTRACT

A 35-year-old, 50-kg female with a history of epilepsy was scheduled for elective breast surgery (fibroadenoma) under general anaesthesia. She was given glycopyrrolate 0.2 mg, ondansetron 4 mg and tramadol 100 mg i.v. as premedication. Within 5 min, she had an acute episode of generalised tonic-clonic seizure that was successfully treated with 75 mg thiopentone i.v. and after 30 min, she was given general anaesthesia with endotracheal intubation. Surgery, intra-operative period, extubation and post-operative period were uneventful. We conclude that tramadol may provoke seizures in patients with epilepsy even within the recommended dose range.

**Key words:** Seizures, serotonin syndrome, tramadol, tramadol-induced seizures

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### INTRODUCTION

Tramadol hydrochloride is a synthetic analogue of codeine used for the treatment of moderate to severe pain. It has a dual mechanism of action. Tramadol and its active metabolite, O-desmethyl tramadol, bind to  $\mu$  opioid receptors thus exerting their effect on GABAergic transmission. They also inhibit reuptake of 5-hydroxy tryptamine (serotonin) and noradrenaline.<sup>[1]</sup> These latter effects are likely to be an important element in analgesia, and may also account for triggering two significant adverse events – seizures and serotonin syndrome.<sup>[2]</sup> These may develop during tramadol monotherapy either at routine<sup>[3]</sup> or excessive doses,<sup>[4]</sup> but are particularly likely during tramadol coadministration with antidepressants<sup>[5]</sup> or in epileptic patients.<sup>[3,6]</sup>

There are a few tramadol-induced seizure reports around the world,<sup>[3,6,7]</sup> and this is the first report in India. We are presenting a case of a 35 year old female with a history of epilepsy who developed generalised tonic-clonic seizures after i.v. injection of tramadol (100 mg) given as premedication before anaesthesia.

### CASE REPORT

A 35-year-old, 50-kg female having fibroadenoma breast was scheduled for elective surgery under general anaesthesia. Preanaesthetic examination was unremarkable except that she had a history of epilepsy since the age of 13 years, when she developed generalised tonic-clonic seizures without aura, followed by unconsciousness. Episode of seizures used to occur at 1–2-month intervals without any known precipitating factor. She was under drug treatment, which she could not name, and seizures were well controlled. She had stopped treatment about 2 years back and had no episode of seizure within the last 5 years.

In the operation theatre, a peripheral i.v. cannula of 18 G was taken on the opposite arm to the operative site and 500 ml Ringer lactate (RL) infusion was started. Multipara monitor having ECG, pulse oximetry and non-invasive BP was attached, which showed BP 132/84 mmHg, HR 90/min and SpO<sub>2</sub> 99%. The patient was premedicated with glycopyrrolate 0.2 mg, ondansetron 4 mg and tramadol 100 mg given i.v. Approximately within 5 min, an episode

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of generalised tonic-clonic seizure occurred without aura, and, immediately, thiopentone 75 mg i.v. was given (anticonvulsant dose is 0.5–2 mg/kg body wt).<sup>[8]</sup> Guedel's airway was inserted to prevent tongue bite and oxygenated with Bains circuit. The seizure episode terminated immediately and she was carefully watched for another 30 min. Her respiration was smooth (RR 15/min), BP was 130/80 mmHg but HR was in the range of 120–140/min. After that, it was decided to proceed for operation. She was anaesthetized with thiopentone 250 mg followed by succinylcholine 75 mg and intubated with a 7.5 mm cuffed endotracheal tube. Anaesthesia was maintained with N<sub>2</sub>O:O<sub>2</sub> in the ratio of 60:40, isoflurane 0.8–1% and intermittent doses of atracurium. Thousand milliliters of RL was given during the intra-operative period. Vitals were maintained throughout and HR settled around 120/min. Phenytoin 200 mg was given as slow i.v. infusion intra-operatively. At the end of surgery, after thorough oral suctioning, residual muscular blockade was reversed with neostigmine 2.5 mg and glycopyrrolate 0.4 mg. She was extubated when she was conscious and had spontaneous respiration and adequate muscle power. She was further oxygenated for 5 min and shifted to the Intensive Care Unit. Phenytoin was continued as 50 mg BD for 3 days. The patient had not agreed to get further investigations (EEG, computed tomography/magnetic resonance imaging, cerebrospinal fluid examination) and was discharged uneventfully.

## DISCUSSION

Tramadol is a commonly prescribed analgesic because it has a low risk of addiction and better safety profile as compared with other opioids.<sup>[9]</sup> Tramadol inhibits serotonin and noradrenaline reuptake that may cause seizures and serotonin syndrome.<sup>[2]</sup> There are controversies about the seizure-inducing effect of tramadol. Some studies have documented that tramadol can only provoke seizures if used in overdoses in patients with existing seizure disorder or when co-administered with antidepressants, alcohol, etc.,<sup>[5,6,10]</sup> while other studies have revealed that tramadol may induce seizures even when it is used as a monotherapy and in recommended doses.<sup>[3,6]</sup> Some reported higher incidence among the elderly,<sup>[2]</sup> while others reported a higher incidence in young male abusers.<sup>[3,10]</sup>

Tramadol-induced seizures have been reported to be generalised tonic-clonic in nature, without auras or focal symptoms,<sup>[3,11]</sup> as seen in the present case. A recent

cross-sectional study<sup>[3]</sup> examined 106 patients who had experienced seizures after ingesting tramadol. All the patients had witnessed generalised tonic-clonic seizures within 12 h of taking tramadol orally not only in supratherapeutic doses (363.2 ± 303.1 mg) but also in recommended doses even as low as 50 mg. More than 80% of their patients had seizure(s) after ingesting recommended doses of tramadol. 13.2% of them had a history of epilepsy, but their seizures were well controlled and they did not have any seizure during 1 year before their evaluation, as found in our case. Tramadol ingestion was considered as a precipitating factor in this group.

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.<sup>[12]</sup>

Similarly, the First Seizure Clinic in Australia is an outpatient service for rapid evaluation and diagnosis of patients with new-onset seizures, where 8.2% of new-onset seizures were accounted to tramadol exposure. They stated that tramadol was the most frequently suspected cause of provoked seizures, and the frequency of tramadol-related seizures suggests that they may be under reported.<sup>[11]</sup>

Mehrpour<sup>[7]</sup> reported two cases of intravenous tramadol-induced seizures and noticed that this epileptogenicity is especially increased in intravenous prescription and association of agitation, tachycardia, confusion and hypertension, suggesting a possible mild serotonin syndrome. In these two cases, early onset of seizure was seen (during i.v. infusion and immediately after i.v. injection of 100 mg of tramadol), as found in our case. They observed an association of seizures with agitation, which was considered to be due to a serotonergic effect, whereas persistent tachycardia (120–140 bpm) was the only associated finding in our case that could be attributed to mild serotonergic action.

On the other hand, some studies were conducted to assess the risk of idiopathic incident seizures among users of tramadol based on data present in the General Practice Research Database in the United Kingdom (10,916 subjects in 1994–96<sup>[13]</sup> and 11,383 subjects in 1996–98<sup>[14]</sup>). Both of them found no increased risk of idiopathic incident seizures associated with exposure to tramadol alone.

We also used tramadol for i.v. premedication in this patient in spite of knowing that she had a history of epilepsy, because we use tramadol as routine in such patients in our centre, and have observed seizures for the first time. In the present case, glycopyrrolate and ondansetron were coadministered with tramadol, which do not usually contribute to seizure; however, extrapyramidal symptoms (oromandibular dystonia, oculogyric crises and limb dystonia) have been reported after ondansetron.<sup>[15]</sup>

Thus, we conclude that i.v. tramadol can induce seizures even in the recommended dose (100 mg), and this potential life-threatening adverse reaction should be considered if tramadol is being given to an epileptic patient.

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