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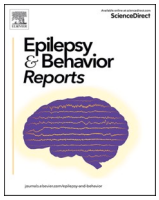

Tramadol use and risk of seizure: A report of two cases and a review of recent literature

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ABSTRACT

Tramadol is a common pain medication used in practice across numerous specialties. Increased incidence of tramadol abuse and overdose in recent decades has led to it being classified as a controlled drug in several countries. Tramadol appears to be an increasingly popular drug of abuse, possibly related to ease of access to it on prescription, and its potential euphoric effects.

We identified two cases of seizures directly related to tramadol exposure. We then reviewed recent literature on tramadol and its adverse effects, particularly looking at its effect on seizure risk and the incidence of seizures. We found that there were scarce recent studies on the relationship between tramadol and seizure risk. Of studies found, many were carried out in animal models. Tramadol-induced seizures were studied in humans more commonly in the context of overdose, and studies involving humans tended to have small patient cohorts and suggested further study in the area.

We suggest that tramadol may be useful as part of multi-modal analgesia in moderate to severe pain in specific contexts, but that greater awareness of its potential adverse effects, and particularly its potential to lower seizure threshold, is warranted. We feel that more readily available information specifically about tramadol's effects on seizure threshold may be of interest to colleagues from any specialty prescribing opioid analgesia on a regular basis, but that colleagues treating patients with seizure disorders should be particularly aware of these potential adverse effects.

1. Introduction

Tramadol is a common pain medication used across numerous specialties. It is a weak μ-opioid agonist, prescribed for moderate to severe pain. It was first introduced in Germany in the late 1970's [1]. Tramadol-related mortality due to abuse and adverse effects has led to it being classified as a controlled drug in several countries [2,3]. Parts of the USA, Australia and Sweden have controlled prescribing of tramadol. It has not been classified as a controlled substance in Ireland and the UK, and remains an over-the-counter medication in India and some south-east Asian countries [1]. Tramadol is becoming an increasingly popular drug of abuse, similar to stronger opioids [1].

We identified two cases of seizures related to tramadol exposure at appropriate therapeutic doses. One in an individual with epilepsy and one without a diagnosis of epilepsy. We reviewed the available literature on tramadol and its adverse effects, particularly looking at seizure risk. Our findings highlight the limited research available on seizure risk with tramadol use outside of the context of overdose. Clearer guidelines and greater awareness of seizure risk is needed when prescribing tramadol for pain.

2. Methods

Two cases were identified in our clinical practice in which tramadol exposure, at an appropriate therapeutic dose, was felt to have caused seizures in both individuals. The connection between tramadol exposure and seizures was assessed using the Naranjo scale and WHO-Uppsala Monitoring Centre (WHO-UMC) causality categories.

Literature reviewed was performed by searching Google Scholar, PubMed and MEDLINE. Articles were selected by our two named authors. English language publications between 2010 and 2023 were reviewed, looking at clinical trials, review articles and case-based articles that studied tramadol and seizure risk. Articles comparing adverse effects from tramadol with other opioids were included in our review,

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looking particularly at seizure risk.

3. Case reports

3.1. Case 1

A 29-year-old female presented following a single bilateral tonic-clonic seizure. She had been well in the period leading up to this seizure and denied any provoking factors such as sleep deprivation, stress, alcohol or illicit drug use. There was no personal or family history of epilepsy and no early life risk factors. There was no causative abnormality found on routine serology, MRI or EEG.

Our patient was taking tramadol for fibromyalgia. She had no other past medical history and was on no other medications. Her tramadol had been recently increased to a dose of 100 mg four times daily, which she was taking regularly in the weeks prior to admission. Toxicology screening was otherwise negative. She was felt to have had a seizure in the context of tramadol use (WHO-UMC category "probable/likely", Naranjo score = 7). She was discharged with a tapering dose of tramadol and commenced on alternative analgesia, and subsequently remained seizure free.

3.2. Case 2

A 76-year-old male, with a background of multiple myeloma and controlled epilepsy, presented following a seizure. Thirty years prior he had been diagnosed with epilepsy. He was on phenytoin for approximately 20 years, which was then ceased by his GP and had remained seizure free off anti-seizure medication for several years.

EEG was normal. MRI showed mild microvascular change. Serology including renal and liver function and electrolytes did not identify any causative abnormalities. Five days prior to this event he was prescribed tramadol 50 mg three times daily for pain. There were no other provoking factors for seizures identified, or potential drug-drug interactions. Tramadol was felt to have provoked his seizure (WHO-UMC category "probable/likely", Naranjo score = 5), and was therefore ceased and he was commenced on levetiracetam. He remained seizure free at his 12-month consultation.

4. Literature review

4.1. Tramadol pharmacology and analgesic effects

Tramadol is metabolised by the liver Cytochrome P450 pathway. Its active metabolite, O-desmethyltramadol, is a μ-opioid receptor agonist with approximately 200-times higher affinity compared to tramadol and is therefore largely responsible for both its analgesic and toxic effects [4]. There is potential for variability in its activity between individuals and drug-drug interactions. An increase in elimination half-life is expected in liver dysfunction, with recommendations to double the interval between doses in these individuals [5].

Phenotypic variations in cytochrome P450 2D6 can be classified as poor metabolisers, intermediate metabolisers, extensive metabolisers and ultrarapid metabolisers. Ultrarapid and extensive metabolisers have approximately 40 % greater serum concentration of active metabolite M1 and experience a stronger opioid response compared to poor metabolisers. Up to 28 % of the populations of North Africa and the Arabian Peninsula are ultrarapid metabolisers, resulting in higher rates of addiction and overdose in these areas. Poor metabolisers have a 20 % higher serum concentration of tramadol, resulting in higher risk of adverse effects such as seizures. Approximately 20 % of Africans, 10 % of European Caucasians and 2 % of Asians are poor metabolisers [6].

Tramadol is not advisable for use in renal impairment, as 90 % of tramadol and its 26 metabolites are eliminated by the kidneys [5]. Doses in renal impairment should be immediate release, and should not exceed 200 mg daily in patients with a GFR of 10–30 ml/min and 100 mg daily in GFR < 10 ml/min or in individuals on dialysis [5]. In patients over 75 years of age, the bioavailability of O-desmethyltramadol increases by 35 % versus those under 40 years of age, and its elimination half-life doubles. The recommendation for elderly patients is to titrate the dose of tramadol based on renal function and not to exceed 300 mg per day [5].

The efficacy of μ-opioids is well documented in management of acute pain and chronic cancer pain, but is less studied in management of chronic non-cancer pain, with potential for adverse effects. Given that the analgesic properties and adverse effects of opioids are mediated by the same type of receptor, it is impossible to completely dissociate their benefit with potentially harmful effects. In tramadol, noradrenaline and serotonin reuptake potentiate the opioid receptor activation [5].

Signs of tramadol toxicity can vary, with the most significant being loss of consciousness, seizures, respiratory depression, serotonin syndrome and death [1,3]. Seizures in particular are more common with tramadol than with other opioids, and can occur at therapeutic doses [1]. Between 1997 and 2017, there were 30,730 cases of tramadol adverse drug reactions reported to the Food and Drug Administration Adverse Event Reporting System, of which seizures accounted for 7 % [6]. Seizures and serotonin syndrome are thought to be secondary to tramadol inhibiting re-uptake of serotonin and noradrenaline [1]. Tramadol can reportedly induce 5-HT release at higher doses and block 5-HT reuptake. Tramadol monotherapy has been reported to cause serotonin syndrome without concomitant serotonergic medications at high doses, but is more likely to occur when combined with other serotonergic agents [7]. In particular care is advised with selective serotonin reuptake inhibitors or serotonin noradrenaline reuptake inhibitors. Serotonin syndrome is a rare and usually dose dependent adverse event in these cases, with many reported cases of serotonin syndrome occurring in overdose. A study by Park et al. suggested that tramadol and serotonergic antidepressants were safe in combination but should be monitored carefully, especially if up-titrating doses or if patients are requiring higher doses of either drug [7].

Tramadol has been known to cause self-limiting tonic-clonic seizures within 6 h of administration [2]. Seizures appear to be dose-dependent but can occur within the recommended treatment range. In tramadol overdose, seizures are reported in over 50 % of patients [3]. Pathways suggested to be involved in tramadol-induced seizures include opioid, histaminergic, glutaminergic and gamma-aminobutyric acid (GABA) receptors. O-desmethyltramadol is known to inhibit GABA-A receptors at high concentrations [2]. Studies have demonstrated benzodiazepines' protective effects in tramadol overdose-induced seizure prophylaxis, attributed to the effect of benzodiazepines on GABA-A/B receptor enhancement [2]. However, increased mortality is also reported in individuals co-ingesting tramadol and benzodiazepines, likely due to cumulative CNS depressive effects [2].

4.2. Animal studies and seizure risk

In animal studies, brain, heart, lung, kidney and liver damage have been associated with high therapeutic and toxic doses of tramadol [5]. Rat models have shown signs of oxidative stress-related apoptosis in the cerebral cortex secondary to chronic tramadol exposure at a dose of 50 mg/kg. Tramadol overdose has been shown to cause congestion, oedema and inflammatory infiltrates in brains of rats [2]. Gholami et al. studied the effects of prenatal tramadol exposure on immature rats and found that tramadol increased the duration of tonic-clonic seizure in comparison to other drugs studied (morphine, methadone and buprenorphine) [8].

Nakhaee et al. studied the effects of naloxone and diazepam in a rat model of tramadol overdose-induced seizure [2]. The number of seizures was significantly higher in the experimental group (i.e., those who received supra-therapeutic doses of tramadol based on weight) compared with the control group. Those who received combined naloxone-diazepam therapy with tramadol had a significant decrease in the number, severity and duration of seizures compared to those who

received tramadol only. Diazepam therapy with tramadol overdose in this study reduced the severity and duration of seizures and increased the number of seizures graded as mild [2].

4.3. Clinical reports and case series

The adverse effect profile of tramadol is highly variable across studies in adult humans, reflecting the wide range of indications, doses and populations studied [5]. Seizures are the most common serious neurological side effect of tramadol use, with an increase in the risk of seizures associated with known seizure disorder or concomitant use of other drugs known to lower the seizure threshold, such as psychotropic medications. Tramadol is contra-indicated in individuals with poorly controlled epilepsy, and should be used with caution and at low doses in all individuals with epilepsy [5]. One case report described a patient who exhibited myoclonus following 5 days of therapeutic dosing of tramadol [9]. The patient studied had no history of seizures and no other cause of myoclonus was found. His symptoms entirely resolved following tramadol cessation. In an accompanying literature review they found that 12 % of drug-induced myoclonus was caused by opioid agents, with 25 % of them being secondary to tramadol use [9]. In cases of tramadol intoxication or overdose, naloxone may be useful in counteracting the opioid toxic effects, but is of no use against the toxic effects of the monoaminergic component, such as seizures [5].

Another case-control study assessing the seizure risk in 11,383 patients exposed to tramadol reported that patients prescribed tricyclic antidepressants and SSRI's were 5–9.4 times more likely to experience seizures compared to patients not prescribed antidepressants. Even controlling for medical comorbidities and concomitant prescription medications, patients prescribed tramadol were 2–6 times more prone to seizures compared to those not on tramadol [6].

One review of tramadol adverse effects mentioned seizures as part of the range of potential side effects of tramadol and compared its safety profile with that of tapentadol, an alternative μ-opioid agonist. Roulet et al. found that clinical trials on the efficacy of tramadol were few and of limited quality, with very few independent and academic trials published [5]. Studies conducted tended to be less relevant to clinical practice, excluding breakthrough dosing and co-administration of non-opioid analgesics or polypharmacy [5].

Kazemifar et al. studied the effects of intralipid emulsion, as an adjunct to standard antidote protocols, on tramadol-induced seizures in 80 consecutive patients who were admitted to their emergency department [3]. Those with previous seizure disorder or multiple drugs ingested were excluded from their study. They found that in their cohort, 56 % of patients had seizures before reaching hospital. The primary outcome of in-hospital seizures occurred in 15 of 40 patients in the control group, compared to 0 of 40 in the treatment group, making their number needed to treat 2.7 (37.5 % absolute risk reduction) [3].

Morrow et al. compared the rates of new-onset seizures in patients who had recently used tramadol, codeine, both or neither, using data from employers or government-sponsored health plans [10]. They excluded any patients with a previous diagnosis of seizures in any context. Seizures requiring evaluation in the emergency department or hospital admissions were studied. Patients receiving tramadol had a 41 % higher risk of seizures in this context compared with those receiving codeine alone [10]. Patients receiving tramadol and codeine also experienced a significantly higher risk of seizures relative to those treated with codeine alone. Patients unexposed to either medication had a lower risk. Higher risk of seizures was observed with highest level of tramadol exposure (defined as $\geq$400 mg daily). No significant association was seen between higher doses of codeine and seizures, when compared with codeine doses of $<$180 mg daily [10].

5. Discussion and recommendations

We describe two cases of seizures that were related to recent tramadol use. One in a patient with a distant history of epilepsy and one without epilepsy. Both patients had seizures in the context of either starting tramadol or increasing their tramadol dose. Both individuals then remained seizure free off tramadol at their outpatient follow up. No other biochemical or pharmacological seizure provokers were identified in either case. Interestingly, both of our patients had seizures in the context of tramadol use at doses considered to be within the appropriate therapeutic range. There was no evidence that they had taken an overdose or any identified reason that they may not have eliminated tramadol effectively.

We found that there were scarce recent studies on the relationship between tramadol and seizure risk. Of studies found, many were carried out in animal models. Tramadol-induced seizures were studied in humans more commonly in the context of overdose, and studies involving humans tended to have small patient cohorts leading to higher risk of bias. Many articles included in our review of literature suggested further study in the area. Studies relating to the risk of seizures at appropriate therapeutic doses of tramadol may also be beneficial, as this was the case with our patients.

In many contexts in which tramadol is studied, non-opioid analgesia would still be the first-line analgesia [5]. Several studies have demonstrated its efficacy in post-operative pain, and it has been recommended as part of a multi-modal approach to analgesia in this context. Possibly contributing to its recommendation in this situation is that it is not a controlled substance in many countries [5]. Studies looking at the role of tramadol in moderate to severe cancer pain were of poor quality due to lack of double-blind designs, small numbers of participants and risk of bias.

Recent literature suggests that tramadol may be useful as part of multi-modal analgesia in moderate to severe pain in specific contexts, but that greater awareness of its potential adverse effects, and particularly its potential to lower seizure threshold, is warranted. Animal studies in particular demonstrate the serious consequences of tramadol-related seizures such as patient morbidity, mortality. We feel that more readily available information specifically about tramadol's effects on seizure threshold may be of interest to colleagues from any specialty prescribing opioid analgesia on a regular basis. Particularly colleagues treating individuals with epilepsy. Tramadol should be considered a potential cause of exacerbation of seizures, or in individuals presenting with a first onset seizure without any other evident provoking factors in their clinical history.

CRediT authorship contribution statement

Emma Dolan: Writing – original draft, Data curation. **Norman Delanty:** Writing – review & editing, Supervision.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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