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Iatrogenic neuropsychiatric syndromes

Background

Although tramadol induced neuropsychiatric toxicity, dependence and withdrawal have been extensively reported in chronic pain sufferers, such cases continue to surface in clinical practice.

Objective

We describe two cases of atypical withdrawal after abrupt discontinuation of tramadol and a case of serotonin syndrome. The outcome was favourable in all three cases.

Discussion

Patients and prescribers are reminded of the risk of severe morbidity including seizures associated with tramadol withdrawal. Serotonin syndrome can be precipitated with tramadol use especially in combination with other serotonergic drugs.

■ **Tramadol is a synthetic, centrally acting analgesic with agonist activity on opioid receptors. It also inhibits the re-uptake of noradrenaline and serotonin in the brain. Tramadol is metabolised in the liver by the cytochrome P450 2D6 and 3A4 enzymes and the active metabolite is excreted in the urine. The half life and clearance of tramadol are altered in patients with severe liver and kidney failure.**

As illustrated by the case studies below, the dosing regimen of tramadol may require adjustment and the analgesic effect may be highly variable. In addition, a modest reduction in tramadol clearance may be seen in general in the elderly due to the physiologic decline in organ functions. Tramadol dependence and withdrawal are not uncommon and have been reported, particularly after abrupt cessation of long term treatment.¹ Tramadol withdrawal resembles opioid withdrawal, however, in some instances atypical neuropsychiatric symptoms including hallucinations, psychomotor agitation and confusion have been reported.¹

Discontinuation of treatment

Case study 1 presented with neuropsychiatric toxicity likely related to sudden discontinuation of longstanding treatment. Use of the Naranjo adverse drug reaction (ADR) probability scale indicated a probable association between observed neurotoxicity and tramadol in both cases.² The Naranjo ADR scale is a questionnaire of 10 questions with yes/no answers. Each answer receives an allocated score of between -1 and +2 with a final numerical score calculated by adding all individual scores. The final calculated numerical score will help assess the likelihood of an ADR: >9 = highly probable, 5-8 = probable, 1-4 = possible, and 0 = doubtful.²

Case study 2 had probable withdrawal seizures, which to our knowledge, has not been previously reported.

Tramadol safety data

Important safety data extending only up to 6 months of use of slow

release preparations shows that tramadol withdrawal was reported as a serious ADR.³

The Drug Abuse Advisory Committee of the USA Food and Drug Administration found that 40% of reported ADRs were related to drug discontinuation, of which 12.5% were atypical neuropsychiatric symptoms.¹ The Australian Drug Reactions Advisory Committee (ADRAC) found over a 4 year period that neuropsychiatric reactions comprised 30% of reported serious ADRs. These included convulsions, hallucinations, confusion and serotonin syndrome.⁴ The American and Australian safety data is relevant in the context of the increasing usage of tramadol worldwide.⁴ It is estimated that in Australia, the Pharmaceutical Benefits Schedule dispensing of oral formulations exceeded 1 million in 2002.⁴

German data shows that dependence, abuse and withdrawal are more common when tramadol is prescribed for chronic pain management.⁵

An analysis of the pattern of use of tramadol in Sweden confirms that abuse is not a negligible phenomenon in patients with chronic pain refractory to other treatments.⁶

Serotonin syndrome

Case study 3 developed serotonin syndrome after a top up dose of tramadol and a newly added serotonergic drug. This patient was previously stable on a combination of medications with potential for serotonin toxicity. In this case the Naranjo score indicated a probable association between serotonin toxicity and the medications.²

The syndrome may develop if drugs with serotonergic properties including selective serotonin or noradrenaline re-uptake inhibitors (SSRIs or SNRIs), tricyclic antidepressants, monoamine oxidase inhibitors (MAOIs) and other serotonin releasing agents such as amphetamines or ecstasy are combined.⁷ It has also been described in patients using only one serotonergic drug, albeit with a lower prevalence.⁸

The diagnosis of serotonin syndrome is clinical and consists of a triad of cognitive behavioural changes, autonomic dysfunction and neuromuscular dysfunction. In severe cases, there may be rapid clinical deterioration and death.

Treatment of serotonin syndrome involves withdrawal of the offending medications and supportive measures. Severe cases may require management in the intensive care setting.⁹ Hydroxytryptamine receptor antagonists including cyproheptadine and chlorpromazine have been used with modest results.

Conclusion

Tramadol is prescribed in many countries for its analgesic properties, however neuropsychiatric ADRs, dependence and withdrawal phenomena including seizures limit its safe use. Chronic pain sufferers with severe liver and kidney failure, patients with a high drug burden including antidepressants, and the elderly, are at risk of developing serious toxicity and withdrawal symptoms. The risks associated with tramadol prescribing should be assessed against other options for chronic pain management.

Case study 1

A man, 61 years of age, presented with a 2 day history of psychomotor agitation after a recent lumbosacral decompression for chronic lower back pain. He had been taking tramadol slow release 200 mg twice per day for many years, which was stopped abruptly 3 days before his presentation.

On examination he was afebrile, his blood pressure was 135/65 mmHg, heart rate 100 beats/min and regular. He did not have any focal neurological deficits and the rest of the examination was unremarkable.

Tramadol immediate release 100 mg/day was restarted with rapid resolution of symptoms. He was discharged on a dose reduction scale.

Case study 2

A woman, 27 years of age, had two witnessed generalised tonic clonic seizures without any history of substance abuse, previous seizures or epilepsy. She had been taking tramadol SR 400 mg twice per day for more than 6 months for intractable right upper quadrant pain. The medication was ceased abruptly after a laparoscopic cholecystectomy and 3 days before her seizures.

On examination she was postictal, normoglycaemic, her blood pressure was 99/48 mmHg, heart rate 100 beats/min and regular and there were no focal neurological deficits. Brain computed tomography and magnetic resonance imaging were normal. An electroencephalogram showed no epileptiform activity. The medication was reintroduced on a dose reduction scale and she had no recurrence of seizures.

Case study 3

A man, 50 years of age, with chronic leg ulcers suddenly became confused and developed psychomotor agitation, visual hallucinations and postural tremor. A screen for acute delirium was noncontributory.

He was taking 26 different medications for type 2 diabetes mellitus, morbid obesity, osteoarthritis and reactive depression. Important neurotoxic drugs included: tramadol 50 mg four times per day, oxycodone 5 mg four times per day, clonidine 150 µg twice per day and fentanyl 50 µg four times per day. Venlafaxine XR 75 mg/day was added recently for reactive depression. He received a top up oral dose of tramadol 100 mg before his deterioration.

On examination his heart rate was 100/min and regular, blood pressure 156/96 mmHg, respiratory rate 24/min and axillary temperature 37.6°C. A neurological examination revealed postural tremor and hyperreflexia.

He was diagnosed with serotonin syndrome, venlafaxine and tramadol were ceased and the symptoms resolved rapidly.

Summary of important points

- Abrupt cessation of long term tramadol use may be complicated by withdrawal syndrome.
- Seizures may be a feature of atypical withdrawal.
- Tramadol in combination with other serotonergic drugs can precipitate serotonin syndrome.
- There are risks associated with long term tramadol use in the management of chronic pain.
- Dosing requires careful consideration in the elderly and those with renal and/or liver failure.

Conflict of interest: none declared.

References

1. Senay EC, Adams EH, Geller A, et al. Physical dependence of Ultram (tramadol hydrochloride): both opioid-like and atypical withdrawal symptoms occur. *Drug Alcohol Depend* 2003;69:233–41.
2. Naranjo C, Busto U, Sellers E, et al. A method for estimation the probability of adverse drug reactions. *Clin Pharmacol Ther* 1981;30:239–45.
3. Malonne H, Coffiner M, Fontaine D, et al. Long-term tolerability of tramadol LP, a new once-daily formulation, in patients with osteoarthritis or low back pain. *J Clin Pharm Ther* 2005;30:113–20.
4. ADRAC. Tramadol: four years experience. *Aust Adv Drug React Bull* 2003;22:1.
5. Cossmann M, Kohnen C, Langford R, McCartney C. Tolerance and safety of tramadol use. Results of international studies and data from drug surveillance. *Drugs* 1997;53(Suppl 2):50–62.
6. Naslund S, Dahlqvist R. Treatment with tramadol can give rise to dependence and abuse. *Lakartidningen* 2003;100:712–4.
7. Isbister GK, Buckley NA, Whyte IM. Serotonin toxicity: a practical approach to diagnosis and treatment. *Med J Aust* 2007;187:361–5.
8. Garrett P. Tramadol overdose and serotonin syndrome manifesting as acute right heart dysfunction. *Anaesth Intensive Care* 2004;32:575–7.
9. Jones D, Story D. Serotonin syndrome and the anaesthetist. *Anaesth Intensive Care* 2005;33:181–7.