

Serotonin syndrome and rhabdomyolysis in venlafaxine poisoning: a case report

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ABSTRACT

Newer, more selective, antidepressant agents are increasingly being used as first-line treatment. However, clinical experience in patients after a deliberate overdose is limited. We present a case of venlafaxine intoxication complicated by a late rise in creatine kinase, seizures and serotonin syndrome. Rhabdomyolysis prolonged the hospital stay in our patient but had no other serious consequences. Physicians should be aware of this late phenomenon in patients with venlafaxine poisoning.

KEYWORDS

Rhabdomyolysis, self-poisoning, serotonin syndrome, venlafaxine

INTRODUCTION

The development of antidepressant medications has proceeded through several historical phases. The older antidepressants such as monoamine oxidase inhibitors (MOAs) and early tricyclic antidepressants (TCAs) affected a wide range of neurotransmitter systems and caused many undesirable side effects. In the late 1980s new classes of more selective antidepressant agents, starting with the selective serotonin reuptake inhibitors (SSRIs) and more recently serotonin noradrenergic reuptake inhibitors (SNaRIs), noradrenergic specific serotonergic antidepressants (NaSSA) and noradrenaline reuptake inhibitors (NaRI) were introduced and are currently

widely used. Because they do not interact with histaminic, muscarinic, adrenergic or cholinergic receptors, they tend to have a more benign side-effect profile and have improved compliance. These newer drugs have proven efficacy and are often considered to be safer.^{1,2} We present a case of an intoxication to the SNaRI venlafaxine (Efexor) complicated by a late rise in plasma creatine kinase (CK) and the serotonin syndrome.

CASE REPORT

A 21-year old white female with a history of depression was admitted to the emergency department five hours after intoxication with the antidepressant venlafaxine. She reported to have ingested a total of 7.8 g of the extended-release formulation. She had not taken any other medications or alcohol. On presentation she was somnolent and disorientated with a Glasgow Coma Scale of 4-6-3. Her pupils were dilated and responsive to light. She was haemodynamically stable with a blood pressure of 147/55 mmHg and a sinus tachycardia of 160 to 170 beats/min. Her rectal temperature was 38.9°C. There were no signs of respiratory distress. During the initial presentation she suffered a tonic-clonic seizure, which responded well to 1 mg of clonazepam. Routine blood analysis was performed and besides a leucocytosis ($19.3 \times 10^9/l$), which returned to normal within three days, no abnormalities were found. She was admitted to the intensive care unit and treatment was started with activated charcoal and a laxative. Two hours after admission she suffered a second tonic-clonic seizure, which was again terminated with a single

dose of clonazepam 1 mg. Throughout the rest of the admission there were no signs of muscle tenderness. Nausea, vomiting and sweating were prominent. The following day her heart rate was 140 beats/min and her body temperature had dropped to 37.8°C. It took another day before she became fully orientated. On the second day her temperature and heart rate returned to normal (<100 beats/min). We did not detect any intraventricular conduction abnormalities.

Initial plasma CK, taken five hours after ingestion, was 43 U/l (normal range 0-50 U/l). Nineteen hours after ingestion, the plasma CK had increased to 13,653 U/l and it rose progressively over the next few days. A peak of 42,340 U/l was measured 41 hours after ingestion (figure 1). Isoenzymes of CK were CK-MM (muscle) 100%, CK-MB 0% and CK-BB (brain) 0%. Maximum troponin level measured on day 2 was 1.6 µg/l (<2 µg/l). Together with the raised CK of 13,653 U/l blood analysis showed a slight increase in creatine level (118 µmol/l). Treatment was started with hydration and bicarbonate infusion. Renal function was at no time affected. After 51 hours, the CK levels started to decrease (34,841 U/l) and after three days of admission in the intensive care unit she was referred to a psychiatric ward. CK level and creatine level at the time of referral were 22,740 U/l and 68 µmol/l, respectively. After seven days on the psychiatric ward the CK level had decreased further to 1276 U/l.

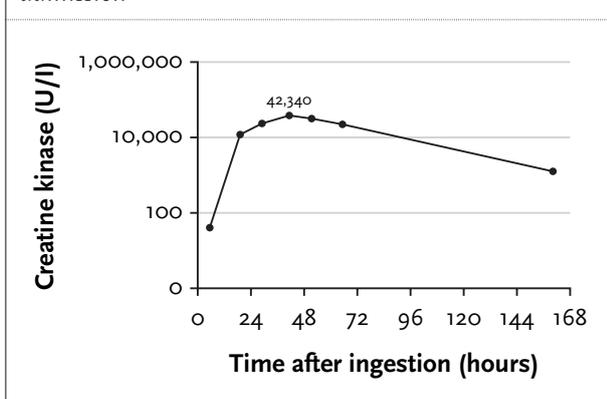
DISCUSSION

Venlafaxine is an antidepressant that causes selective inhibition of neuronal reuptake of serotonin and nor-epinephrine with little effect on other neurotransmitter systems. It is less prone to cause anticholinergic symptoms and sedation than tricyclic antidepressants (TCAs). Venlafaxine is well absorbed and extensively metabolised

in the liver by cytochrome P450 enzyme system. Because of genetic polymorphisms, the metabolism of venlafaxine varies between patients. O-desmethylvenlafaxine (ODV) is the only major active metabolite. The half-lives of the extended-release formulations of venlafaxine and ODV are approximately five hours and 11 hours, respectively. The primary route of excretion of venlafaxine and its metabolites is renal elimination. The most common adverse effects are nausea, asthenia, dizziness, insomnia, somnolence, headache, dry mouth, sweating, hypotension, hypertension, nervousness and abnormal ejaculation.¹³ Several cases of seizures indicating neurological toxicity, tachycardia and QRS prolongation indicating cardiac toxicity as well as serotonin syndrome have been reported following a venlafaxine overdose.^{4,6} The serotonin syndrome is a potentially life-threatening disorder of excessive serotonergic activity. It presents as a triad of altered mental status, neuromuscular abnormalities, and autonomic dysfunction.⁷ It occurs most frequently when two serotonergic agents are given in combination, but may also occur with a single agent.⁸ The patient reported in this case report had clinical signs and symptoms of an altered mental status, autonomic disorders (tachycardia, pupillary dilatation, nausea, hyperthermia and sweating) and a neurological disorder (seizures). Guided by the Sternbach criteria,⁹ the diagnosis of the serotonin syndrome was made in our patient. Therapy is supportive and symptoms usually resolve after discontinuing the offending agent. The raised plasma CK reported in our patient is most likely to have originated from skeletal muscle. It is conceivable that the seizures might account for some of the CK rise, but the magnitude and late peak levels suggest another mechanism as well. Troponin levels were not elevated. A late rise in CK level has previously been reported with a peak CK level of 10,475 U/l four days after ingestion and also without renal impairment.¹⁰ The mechanism of this rare complication of a venlafaxine overdose remains to be elucidated.

A venlafaxine overdose may be more serious than an overdose with SSRIs. An analysis in the United Kingdom of deaths per million prescriptions due to acute single drug poisoning, the so-called fatal toxicity index (FTI), suggested that the FTI of venlafaxine was significantly higher than that of SSRIs and similar to some tricyclic antidepressants.¹¹ Concerns have also been raised that venlafaxine may increase the risk of suicidal ideation and behaviour.¹² In 2004, the US Food and Drug Administration (FDA) asked manufactures to make labelling changes to include a warning about a possible increased risk of suicidality.¹³ Due to the large distribution volume of venlafaxine, forced diuresis, dialysis, haemoperfusion and exchange transfusion are of no benefit. Activated charcoal should be administered to prevent absorption and might be

Figure 1 Plasma concentrations during hospital admission



useful when administered timely. No specific antidotes are known.

The increase in the plasma CK concentrations prolonged the hospital stay for our patient, but had no other serious consequences. Our case serves to illustrate some of the consequences of venlafaxine overdose, such as seizures and serotonin symptoms. In addition, venlafaxine can cause a delayed rise in plasma CKs. Physicians should be aware of this late phenomenon.

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