

Rhabdomyolysis Induced by an Increase in Venlafaxine Dose

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Venlafaxine is a serotonin (5-hydroxytryptamine [5-HT])–norepinephrine reuptake inhibitor used to treat patients with depressive or anxiety disorders. In the United States and France, venlafaxine is initiated at 37.5–75.0 mg, with a maximum dose of 225 mg per day (1, 2). Hepatic cytochrome P450 2D6 (CYP2D6) metabolizes approximately 70% of venlafaxine into desvenlafaxine (O-desmethylvenlafaxine), although both molecules have been reported to have similar effects on the brain (3). At low doses (up to 75 mg), venlafaxine inhibits 5-HT reuptake alone, whereas higher doses (up to 225 mg) cause norepinephrine reuptake inhibition. Although adverse effects of venlafaxine are relatively common (nearly 10%), the most serious ones, which include serotonin syndrome, neuroleptic malignant syndrome, and suicide, are rare (4). Rhabdomyolysis is a less well-known adverse effect that has been described in cases of overdose or pharmacological interactions. A recent review identified only a dozen such cases (5). Most of these cases were attributed to overdose (seven of 12 cases), four cases involved patients with concomitant medications or medical history (e.g., McArdle disease or Parkinson's disease), and only one case involved a patient without any previous medical conditions. However, this patient was described in a study published in a Chinese journal (6) that is not accessible through conventional search engines.

The present report describes a case of a young man who exhibited rhabdomyolysis during escalation of venlafaxine monotherapy initiated according to current guidelines. The case highlights challenges for diagnosis, ambulatory

care, and withdrawal symptoms upon venlafaxine discontinuation. To the best of my knowledge, this is the first case in the English-language medical literature in which no comorbid condition, drug association, or venlafaxine overdose caused rhabdomyolysis as an adverse effect (5).

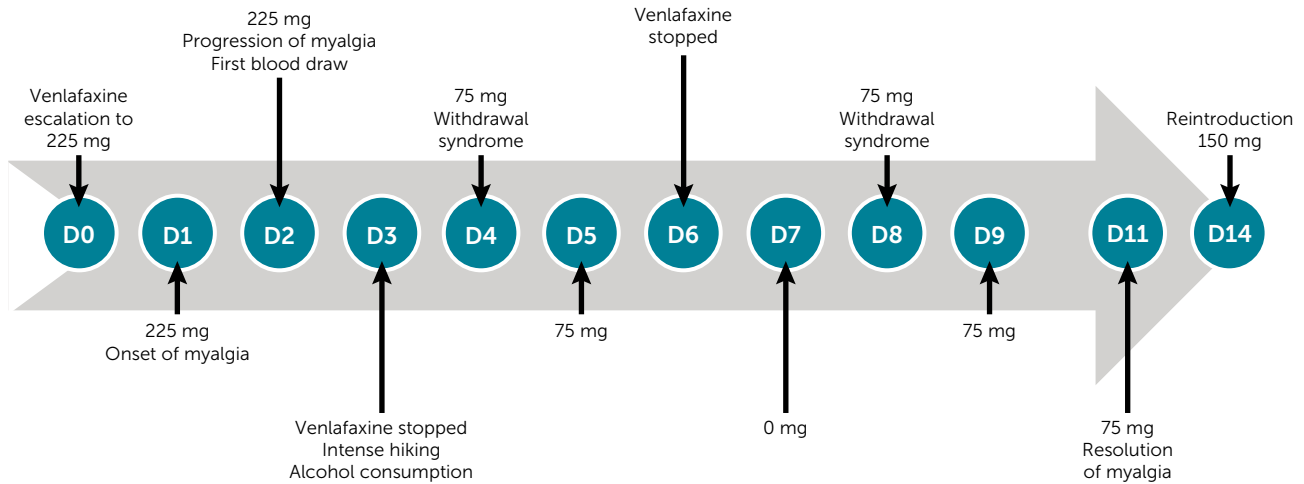
CASE PRESENTATION

Mr. B was a 20- to 30-year-old man with no general medical or psychiatric history of an anxiety or a depressive disorder, who was treated solely in an ambulatory setting and was evaluated for rebound anxiety symptoms. His past treatments included sertraline, up to 200 mg per day, which yielded favorable outcomes during the initial months of treatment until rebound anxiety prompted a switch to venlafaxine, up to 150 mg per day, for the past 5 months. Reported adverse effects were increased sweating and delayed orgasm; however, these adverse effects were deemed not to be severe enough to justify switching the medication. The patient's anxiodepressive symptoms were reduced to nearly baseline levels. Apart from occasional alcohol consumption and electronic cigarette use, no substance use was reported, and the patient received no concomitant treatment. The patient practiced sports for 12 hours per week. His medical and family histories indicated no muscular problems.

The rebound anxiety occurred without any reported trigger and prompted an increase in the venlafaxine dose to 225 mg per day, according to current guidelines (Figure 1). On day 1 of dose escalation, the patient reported stiffness in his pectoral muscles, even though he

had not done any strength training or any other sport in the days prior. On day 2, the stiffness reached his dorsal muscles, prompting a standard blood analysis (Table 1). The results of his laboratory workup were normal, apart from a creatine phosphokinase (CPK) level >10,000 U/L (normative range 200 U/L) and aspartate aminotransferase (AST) levels that were five times higher than normal (normative range <40 U/L). The results revealed no unusual urine coloration, no decrease in renal function, and no evidence of inflammatory syndrome. The patient's electrocardiogram (ECG) and blood ions were normal. Investigations for myoglobinuria were not performed. The patient engaged in physical activity and consumed alcohol on day 3, and he received the results of his blood tests on day 4. His physical activity at the time was hiking, and he reported these activities as being intense on his lower body but compatible with his usual sport practices. His alcohol consumption was reported as 8–10 units (64–80 g of pure alcohol) over a 10-hour period. The patient abruptly discontinued venlafaxine on day 3 because the increase in the venlafaxine dose coincided with myalgia and given that a possible diagnosis of rhabdomyolysis had been discussed with the patient. An immediate tapering off the medication before receiving the laboratory results was not warranted because of the rareness of venlafaxine-induced rhabdomyolysis and the lack of changes in renal function. On day 3, the patient did not report any withdrawal symptoms. On day 4, he reported a decrease in torso stiffness, but pain was present in both upper arms. Headache and dizziness occurred in the afternoon, which

FIGURE 1. Timeline of rhabdomyolysis symptoms and venlafaxine doses for a patient with venlafaxine-induced rhabdomyolysis^a



^a Day 0 (D0) represents venlafaxine escalation to 225 mg per day for rebound anxiety. All doses shown are per day.

the patient recognized as withdrawal symptoms. He therefore decided to take 75 mg of venlafaxine on days 4 and 5. On day 5, a blood analysis revealed a slight decrease in his CPK level (9,700 U/L) and an increase in AST and alanine aminotransferase levels. Over the next days, CPK and AST levels steadily decreased, reaching baseline levels on day 9. Withdrawal symptoms upon venlafaxine discontinuation (headache, dizziness, and nausea) and the decrease in CPK levels prompted the reintroduction of 75 mg venlafaxine from day 8 forward. The patient's stiffness symptoms had resolved by day 11.

An absence of renal failure, the patient's treatment adherence, and regular blood analysis allowed an ambulatory follow-up. Abundant oral hydration was used to address the rhabdomyolysis symptoms. Given the withdrawal syndrome experienced by the patient, the ongoing yet decreasing rhabdomyolysis symptoms caused by the 225-mg venlafaxine dose, and because no recommendations prohibit venlafaxine reintroduction after the observed events, venlafaxine was increased to 150 mg per day on day 14, without recurrence of muscular symptoms. The patient did not report any recurrence in anxiety

symptoms. A reevaluation together with the patient was planned to determine whether to switch from venlafaxine to another psychotropic medication some time after this acute event, depending on the persistence of the original rebound anxiety symptoms. A few weeks later, the patient did not report any residual anxiety symptoms or any new adverse effects, and the decision was made by the treating physician along with the patient to continue with a daily dose of 150 mg venlafaxine.

The primary physical symptom was myalgia, which could be explained by physical exercise. The patient was familiar with postexercise stiffness, and he performed no excessive physical activity before onset of the muscle pain. Known causes of rhabdomyolysis, such as statins and illicit drug use, were ruled out. Thoracic pain may be due to heart or pulmonary diseases, but no other symptoms supported these hypotheses, and the patient's ECG was normal. No biological inflammatory syndrome or symptom suggesting a viral or bacterial infection was identified. Serotonin syndrome and neuroleptic malignant syndrome were ruled out because of the lack of nonmuscular symptoms. Auto-immune conditions, such as polymyositis or dermatomyositis, were also ruled out given the lack of a family history, the physical symptoms being limited to myalgia without dermatological involvement, and the rapid recovery upon reduction in the venlafaxine dose.

TABLE 1. Blood analysis results for a patient with venlafaxine-induced rhabdomyolysis^a

Test	Day 2	Day 5	Day 8	Day 9	Day 16
Leukocytes (g/L)	9.5	5.6	5.2	5.8	6.6
Neutrophils (g/L)	6.7	3.4	3.3	3.4	3.7
Potassium (mMol)	3.6	4.4	4.3	4.4	3.9
Calcium (mMol)	2.3	2.4	2.5	2.5	2.4
C-reactive protein (mg/L)	0.6	—	—	—	—
AST (U/L)	243 ^b	511 ^b	146 ^b	94 ^b	—
ALT (U/L)	46 ^b	130 ^b	90 ^b	75 ^b	—
GGT (U/L)	11	11	9	11	—
ALP (U/L)	109	102	108	100	—
CPK (U/L)	10,299 ^b	9,703 ^b	1,048 ^b	677 ^b	122
Creatinine (μMol)	92	92	91	89	96

^a Dashes indicate unmeasured variables. ALP=alkaline phosphatase (normative range <130 U/L); ALT=alanine aminotransferase (normative range <45 U/L); AST=aspartate aminotransferase (normative range <40 U/L); CPK=creatinine phosphokinase (normative range <200 U/L); GGT=gamma-glutamyl transferase (normative range <45 U/L).

^b Abnormal values.

DISCUSSION

In the present case, a patient experienced rhabdomyolysis after an escalation in venlafaxine dose within current recommendations. Rhabdomyolysis is a serious condition for which clear treatment recommendations exist for inpatients, particularly when it is caused by traumatic injuries (7, 8). However, the present case highlights the need for clearer guidelines for outpatients experiencing adverse effects of medication dose adjustments in response to an onset of rhabdomyolysis. Withdrawal syndrome is common with venlafaxine (9, 10), and in this case prevented discontinuation of the medication. The patient restarted venlafaxine at a low dose on his own, and a discussion of the risks and benefits of the medication between the patient and treating physician prompted resumption of venlafaxine treatment at 150 mg per day after full recovery from the rhabdomyolysis symptoms. No adverse effects were reported with this lower dose. Regarding the absence of rebound anxiety upon venlafaxine discontinuation, withdrawal symptoms were probably masking any psychiatric symptoms. The patient was reevaluated a few weeks after these acute events, and he did not report any recurrence of the original rebound anxiety. The decision was made to continue venlafaxine at 150 mg per day.

The serotonergic action of venlafaxine was probably the cause of the observed adverse effects in this case, although the underlying physiopathology is incompletely understood. Increase in intracellular calcium levels after activation of 5-HT receptors could induce various cellular mechanisms that may lead to muscular cell death (11–13). CYP2D6 hepatic metabolism was not expected to play a role in the observed symptoms, because both venlafaxine and desvenlafaxine are reported to have similar effects on brain 5-HT receptors (3). In this regard, differences between central and peripheral activities of these receptors cannot be discounted. However, higher doses (i.e., ≥ 150 mg per day) of venlafaxine exert a lesser effect on the serotonergic system and a greater effect on the norepinephrinergic system. In this

KEY POINTS/CLINICAL PEARLS

- Clinicians should inform patients of potential adverse effects of venlafaxine upon treatment commencement or any change in dosage.
- Patients' daily activities (such as high-intensity sports) should be considered an etiology of last resort.
- Venlafaxine withdrawal syndrome should be considered in cases when abrupt discontinuation of the medication is needed.
- Clear guidelines for discontinuing venlafaxine in cases when this medication is suspected to have caused rhabdomyolysis are lacking.

case, rhabdomyolysis occurred at 225 mg per day, prompting the question of whether norepinephrine may be implicated in the condition. Indeed, findings from studies on methamphetamine-derived drugs (14, 15) indicate that both catecholaminergic and serotonergic signaling pathways may play a role in drug-induced rhabdomyolysis. Overall, this case and the broader literature highlight the need for further research to enhance understanding of medication-induced rhabdomyolysis.

The absence of guidelines regarding medication-induced rhabdomyolysis rendered the medical decisions in this case difficult. In particular, it was unclear whether an abrupt venlafaxine taper was necessary to protect the patient's kidneys, considering the potential downside that venlafaxine withdrawal may cause significant discomfort for the patient. Whether an abrupt discontinuation would justify hospitalization was also difficult to evaluate. Venlafaxine-induced rhabdomyolysis is rare; as a result, patients and clinicians are seldom alerted to the possibility that rhabdomyolysis is a potential adverse effect of this medication. This case study emphasizes the vital importance of providing patients with comprehensive information about potential adverse effects of venlafaxine and their symptoms, both at the start of venlafaxine treatment and during any dose adjustments.

Dr. Aydin is a first-year resident in psychiatry at the Université Paris Cité, Paris.

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The author confirms that details of the case have been disguised to protect patient privacy. Institutional review board approval was not required for this study.

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