12. Saunders MD, Kimmey MB. Systematic review: acute colonic pseudo-obstruction. *Aliment Pharmacol Ther*. 2005;22:917–925.

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D-Dimer Elevation in Asymptomatic Vascular Disease After Venlafaxine Administration

To the Editors:

Venlafaxine is a serotonin-norepinephrine reuptake inhibitor. In addition to the antidepressant effect of venlafaxine, it also relieves nonorganic physical pain.[1] D-dimer is a soluble fibrin degradation product that results from ordered breakdown of thrombi by the fibrinolytic system, and D-dimer serves as a valuable marker of activation of coagulation and fibrinolysis.[2] Serum D-dimer testing can help diagnose deep vein thrombosis (DVT) or pulmonary embolism (PE).[3] It was reported that tricyclic antidepressants can cause DVT or PE. We here report a patient with D-dimer elevation and asymptomatic vascular disease after venlafaxine administration.

We reported the patient was a married and retired 71-year-old woman. Height 163 cm, weight 62 kg, body mass index 23.3 kg/m^2. She was complaining of sadness for 2 months, which had been aggravated in the past 2 days. Venlafaxine 150 mg/d had been administered at 8:00 A.M. She denied a history of any serious organic diseases. Her vital signs were stable, and the overall physical examination was normal. Venlafaxine had been continued to improve the depressive mood. Emergency blood tests were performed, including hematology, C-reactive protein test, serum biochemical test, and functional blood coagulation and D-dimer test. Myocardial enzymes, including cTnI test, were also assessed, and no significant abnormalities were found, except for a D-dimer level of 1190.0 μg/L, blood platelet (PLT) level of 218 × 10^9/L, prothrombin time (PT) of 10.5 seconds, activated partial thromboplastin time (APTT) of 24.1 seconds, and fibrinogen (FIB) level of 2.57 g/L.

Three days after admission, an arterial and venous color Doppler ultrasonography was performed, showing multiple small plaques in both lower limb arteries. Venlafaxine dosage was increased to 225 mg/d and functional blood coagulation and D-dimer tests were assessed 1 week later and showed a PLT level of 225 × 10^9/L, PT of 10.8 seconds, APTT of 24.3 seconds, FIB level of 2.69 g/L, and D-dimer of 7890.0 μg/L. These tests were repeated the next day and showed a PLT level of 220 × 10^9/L, PT of 10.8 seconds, APTT of 23.3 seconds, FIB level of 2.43 g/L, and D-dimer of 8490.0 μg/L. The patient developed occasional pain and swelling of the left lower limb, and the emergency arterial and venous color Doppler ultrasonography indicated multiple small plaques in both lower limb arteries, with normal blood flow in the deep veins of both lower limbs, and a thrombosis in the medial great saphenous vein of left thigh. Enoxaparin sodium injection 4000 IU every 12 hours was immediately administrated for anticoagulation therapy. The next day, an enhanced pulmonary CT angiography scan was performed, showing no obvious abnormalities. The final diagnosis is single episode depressive disorder (Hamilton Rating Scale for Depression, 35). The patient underwent surgery was scheduled to repair the varicosis of the great saphenous vein in the left lower limb 3 days later.

One month later, the patient presented to the clinical psychology clinic for a routine follow-up examination. Functional blood coagulation and D-dimer tests showed a PLT level of 228 × 10^9/L, a PT of 10.5 seconds, APTT of 23.8 seconds, FIB level of 2.39 g/L, and D-dimer of 3490 μg/L. A week after venlafaxine was discontinued, a telephone follow-up indicated that the D-dimer had decreased, functional blood coagulation and D-dimer tests showed a PLT level of 231 × 10^9/L, a PT of 10.4 seconds, APTT of 23.3 seconds, FIB level of 2.65 g/L, and D-dimer of 1110.0 μg/L. One month later, coagulation function, functional blood coagulation, and D-dimer tests were performed again and showed a PLT level of 239 × 10^9/L, a PT of 11.1 seconds, APTT of 24.3 seconds, FIB level of 2.61 g/L, and D-dimer of 6150.0 μg/L as the patient resumed venlafaxine a week ago. The patient was advised to stop venlafaxine immediately. A week later, the D-dimer level was decreased and showed a PLT level of 223 × 10^9/L, a PT of 10.3 seconds, APTT of 23.8 seconds, FIB level of 2.46 g/L, and D-dimer of 650.0 μg/L.

We received written publication consent from the subject for publication of this case report. Institutional review and ethics boards consent for research was obtained.

Chronic diseases such as depression and anxiety are major killers in the modern era. Physical inactivity is a primary cause of most chronic diseases.[4] Depression in elderly people is considered a risk factor for venous thromboembolism (VTE).[5] The main symptoms of depression include psychomotor inhibition resulting in significantly prolonged sleeping described in the "*Diagnostic and Statistical Manual of Mental Disorders*," which could be an important risk factor for venous embolism. Lederbogen et al[6] conclude that major depression is associated with increased platelet aggregability, which seems to persist even under a marked improvement in depressive symptom. In a study by Hoirisch-Clapauch et al,[7] tissue plasminogen activator and plasminogen activator inhibitor 1 imbalance may play an important role in pathophysiology of mental and thromboembolic disorders. Tissue plasminogen activator facilitates clot dissolution and participates in several brain functions, including response to stress, learning, and memory.[7] Parkin et al[8] showed that women with antidepressant use had a significantly higher risk of VTE than women who reported neither depression nor use of psychotropic drugs. Venous thromboembolism risk was not significantly increased in women who were treated for depression or anxiety, without use of antidepressants or other psychotropic drugs. A few studies have shown that many depressive patients on long-term antidepressants had elevated D-dimer levels with asymptomatic venous embolisms.[9] At present, the pathogenesis underlying antidepressant-induced DVT or PE is unclear, Öhlinger et al[10] found that TMEM16F inhibitors tannic acid and epigallocatechin-3-gallate inhibit lipid mediator lysophosphatidic acid–induced phosphatidylserine exposure and calcium uptake at low micromolar concentrations; fluoxetine, an antidepressant and a known activator of TMEM16F, enhances these processes. Erythrocytes actively modulate blood clotting and thrombus formation.[10] In addition, doxepin is a powerful inhibitor of collagen receptor glycoprotein VI-dependent platelet Ca^{2+} signaling, platelet activation, and thrombus formation.[11] Most recent studies have examined DVT or PE caused by antipsychotic drugs,[12] such as clozapine.[13] To our knowledge, no studies on D-dimer elevations, DVT, or PE caused by dual-receptor antidepressants have been reported. Medications and D-dimer changes in the patient are shown in Figure 1.

We used the Naranjo Scale to assess the relationship between the possible adverse event and venlafaxine. There were no previous conclusive reports on this adverse reaction. This case report described the possible adverse event associated with D-dimer elevations after administration of venlafaxine in patients with depression. In addition, this adverse event improved when venlafaxine was discontinued. When venlafaxine was readministered, D-dimer elevations again. The patient has never taken antidepressants or antipsychotics before. The patient was not taking other antidepressants after discontinuing venlafaxine during the illness. There are many reasons for the increase of D-dimer, such as sepsis, malignancy, trauma, cerebrovascular accident, and so on.[14] In addition, being overweight, aging, and depression can also lead to elevated D-dimer. In this case report, the patient was an elderly depression patient with a BMI in the normal range, among which

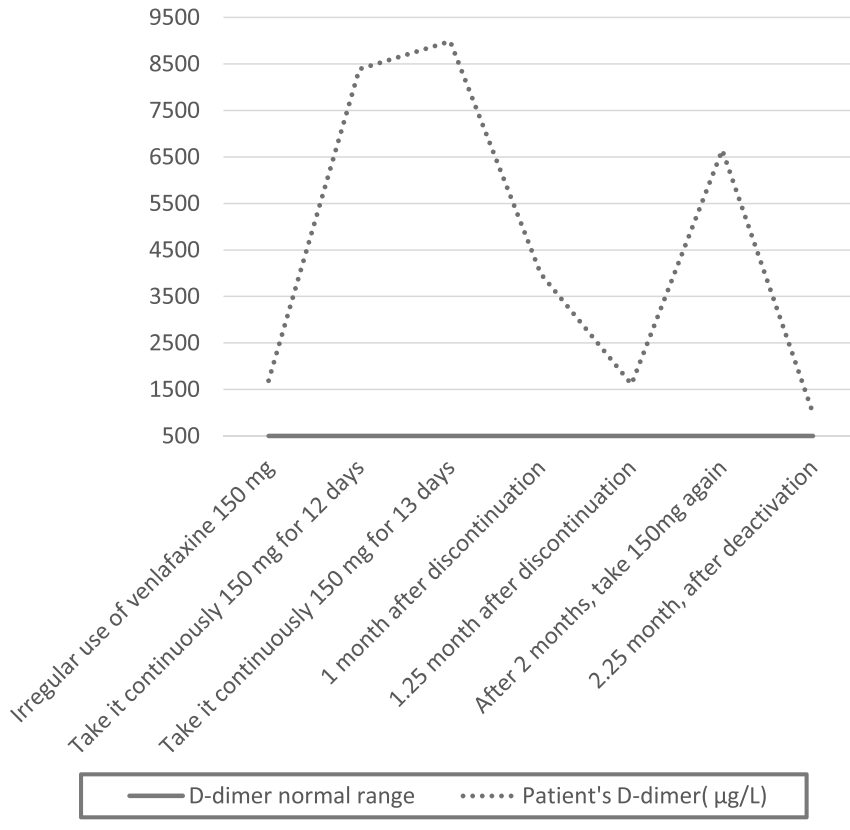

FIGURE 1. Medications and D-dimer changes in the patient.

older age and depression were potential factors for elevated D-dimer. According to a study by Naranjo et al,[15] the patient's ADR score was 5. (The ADR was assigned to a probability category from the total score as follows: definite ≥9, probable 5–8, possible 1–4, doubtful ≤0[15]). Thus, we think that DVT or PE should be ruled out initially in patients taking long-term venlafaxine for mild depressive symptoms. Functional blood coagulation and D-dimer tests, as well as venous color Doppler ultrasonography, and enhanced pulmonary CT angiography should be routinely performed, whether in an outpatient or inpatient setting, to enhance the early detection and treatment of vascular disorders in patients taking venlafaxine for depression.

AUTHOR DISCLOSURE INFORMATION

The authors declare no conflicts of interest.

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REFERENCES

1. Attal N. Pharmacological treatments of neuropathic pain: the latest recommendations. *Rev Neurol (Paris)*. 2019;175:46–50.
2. Weitz JI, Fredenburgh JC, Eikelboom JW. A test in context: D-dimer. *J Am Coll Cardiol*. 2017;70:2411–2420.
3. Di Nisio M, van Es N, Büller HR. Deep vein thrombosis and pulmonary embolism. *Lancet*. 2016;388:3060–3073.
4. Booth FW, Roberts CK, Laye MJ. Lack of exercise is a major cause of chronic diseases. *Compr Physiol*. 2012;2:1143–1211.
5. Siguret V, Emmerich J, Belleville T, et al. Prevalence of hereditary thrombophilia in patients older than 75 years with venous thromboembolism referred for thrombophilia screening. *J Gerontol A Biol Sci Med Sci*. 2015; 70:977–981.
6. Lederbogen F, Gilles M, Maras A, et al. Increased platelet aggregability in major depression? *Psychiatry Res*. 2001;102: 255–261.
7. Hoirisch-Clapauch S, Nardi AE, Gris JC, et al. Mental disorders and thrombotic risk. *Semin Thromb Hemost*. 2013;39:943–949.
8. Parkin L, Balkwill A, Sweetland S, et al. Antidepressants, depression, and venous thromboembolism risk: large prospective study of UK women. *J Am Heart Assoc*. 2017; 6:e005316.
9. Takeshima M, Ishikawa H, Umeta Y, et al. Prevalence of asymptomatic venous thromboembolism in depressive inpatients. *Neuropsychiatr Dis Treat*. 2020;16: 579–587.
10. Öhlinger T, Müllner EW, Fritz M, et al. Lysophosphatidic acid-induced prothrombotic phosphatidylserine exposure and ionophore-induced microvesiculation is mediated by the scramblase TMEM16F in erythrocytes. *Blood Cells Mol Dis*. 2020; 83:102426.
11. Geue S, Walker-Allgaier B, Eißler D, et al. Doxepin inhibits GPVI-dependent platelet Ca^{2+} signaling and collagen-dependent thrombus formation. *Am J Physiol Cell Physiol*. 2017; 312:C765–C774.
12. Farah RE, Makhoul NM, Farah RE, et al. Fatal venous thromboembolism associated with antipsychotic therapy. *Ann Pharmacother*. 2004;38:1435–1438.
13. Hägg S, Jönsson AK, Spigset O. Risk of venous thromboembolism due to antipsychotic drug therapy. *Expert Opin Drug Saf*. 2009; 8:537–547.
14. Tang N, Pan Y, Xu C, et al. Characteristics of emergency patients with markedly elevated D-dimer levels. *Sci Rep*. 2020; 10:7784.
15. Naranjo CA, Busto U, Sellers EM, et al. A method for estimating the probability of adverse drug reactions. *Clin Pharmacol Ther*. 1981;30: 239–245.