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Lethal Acute Colonic Pseudo-Obstruction in a Patient Using a Combination of Olanzapine and Clozapine

To the Editors:

Clozapine is an effective antipsychotic for therapy-resistant schizophrenia. Well-known adverse effects that are strictly monitored include agranulocytosis and metabolic side effects (diabetes, dyslipidemia, and adipositas). Clozapine has antidopaminergic, noradrenolytic, and antihistaminic affinity but is a potent anticholinergic and antiserotonergic agent as well. Olanzapine is another, closely related, atypical antipsychotic agent with partially overlapping chemical structure and similar receptor binding profile to clozapine. Use of either of these antipsychotics can, mainly because of the anticholinergic effect, lead to gastrointestinal adverse effects, such as gastrointestinal hypomotility. Clozapine-induced gastrointestinal hypomotility (CIGH) can lead to Ogilvie syndrome, which is the acute and massive dilation of the colon (colonic pseudo-obstruction). Reported mortality rates in clozapine users with Ogilvie syndrome range from 15%[1] up to 43.7%,[2] approximately 12 times higher than agranulocytosis-related mortality.[3–5] The high mortality rates may partly be due to late diagnosis because of poor awareness of these adverse effects and atypical presentation of symptoms. In this report, we describe a case of acute colonic pseudo-obstruction with fatal outcome during a switch from olanzapine to clozapine. The goal of this article is to increase awareness of CIGH.

Written consent to publish the report has been obtained from the patient's father.

CASE REPORT

A 23-year-old man was involuntarily admitted to the psychiatric ward, because of a first psychotic episode. The patient was aggressive and sexually disinhibited, elicited by acoustic hallucinations. His thinking and behavior were disorganized. The patient finished high school but never finished higher professional education. Social withdrawal was present for 4 years. The patient was a nonsmoker and there was no substance use. In the patient's somatic history, there was a Schwannoma resection at age 13 years. A magnetic resonance imaging–brain after admission showed no changes compared with the magnetic resonance imaging after resection. The family history showed that his uncle also had psychotic episodes.

The patient's symptoms barely responded to haloperidol orally (up to 7 mg) after 2 weeks. We switched to olanzapine orally (up to 25 mg) with partial response after 4 weeks. The increase from 20- to 25-mg olanzapine showed little improvement and the patient's mental condition was precarious. Therefore, we decided to start with clozapine. The olanzapine was continued at 20 mg, while clozapine was started at 12.5 mg once daily orally (day 1) and increased to 25 mg once daily after 2 days. The patient did not use any other medication at that moment. Subsequently, the clozapine was increased with 25 mg/d every 2 days. Supplemental Appendix 1, http://links.lww.com/JCP/A825, provides a timeline. The olanzapine was continued at 20 mg and later decreased to 15 mg (day 21), because the disinhibition and aggression decreased, but the psychotic symptoms were still severe. Clozapine was increased to 250 mg at day 21 (serum levels were 146 μg/L of clozapine and 83 μg/L of *N*-desmethylclozapine [norclozapine; reference values: clozapine, 350–700 μg/L and *N*-desmethylclozapine 100–600 μg/L, measured 13 hours after a gift of 250 mg], Supplemental Appendix 1, http://links.lww.com/JCP/A825 shows all serum levels). The patient ate well, moved without discomfort, reported no pain or constipation and he repeatedly reported that he had passed stool. He went home to his family for a leave of absence, where he also ate well and was physically active without discomfort. The day after he came back to the hospital, he complained of nausea and vomiting. On physical examination, there were no alarm symptoms. During the day, the patient became more psychotic. He reported no pain nor made a painful impression and was ambulant. In the evening, the patient started to vomit repeatedly. He reported that he had passed stools an hour before. He briefly lost consciousness around this time. Clozapine and olanzapine were discontinued. The surgeon examined the patient and found a distended but nontender abdomen with normal peristaltic sounds. A computed tomography scan of the abdomen was made, which showed a dilated colon (caecum 11 cm) and rectum, due to fecal impaction, with no signs of ischemia, perforation, or bowel obstruction beside the fecal impaction. Returning to the ward, the patient severely deteriorated: he started complaining of abdominal pain and he fainted after which he had an impalpable pulse and absent cardiac sounds, although still breathing. Cardiac compressions were started. Abdominal examination now showed an extremely distended and tense abdomen and a cardiac ultrasound showed caval and cardiac hypovolemia. After the patient was put in left tilted position to decompress the caval vene, his pulse recovered. He was sedated and intubated, and he was transferred to the intensive care unit for further stabilization. For gastrointestinal decompression, a rectum cannula and a sucking nasogastric tube were placed, and the patient received fluid resuscitation, intravenous antibiotic treatment with ceftriaxone, ciprofloxacine, and metronidazole, and intravenous noradrenalin. After a short stabilization in the intensive care unit, he was taken for decompressive laparotomy. The colon was necrotic, and a subtotal colectomy was performed. Postoperatively, the patient again transiently stabilized but deteriorated again the next morning. A second-look laparotomy was proceeded where 30 cm of ischemic terminal ileum was removed. The abdominal wall was left open with a bridging Vicryl mesh to keep the intestines visible. The situation worsened in the evening, and again, 40 cm of ischemic ileum, an ischemic sigmoid, and a necrotic gallbladder were resected and an end ileostomy was created. However, severe hemodynamic instability persisted despite high doses of noradrenalin, vasopressin, enoximone, and methylene blue. Overnight the clinical situation deteriorated with multiorgan failure, including liver failure, anuric acute kidney injury, vasoplegia, and progressive rhabdomyolysis. There were no further treatment options, and the patient died.

DISCUSSION

Gastrointestinal hypomotility can occur at any time during treatment with clozapine or olanzapine and monitoring during the

whole treatment is necessary. Palmer et al[3] identified recent start of clozapine, concomitant anticholinergic use, high serum levels, and comorbid illness as risk factors for gastrointestinal hypomotility in clozapine users. The first two were present in our patient. Dome et al[6] described a similar case of an elderly patient receiving a combination of clozapine and olanzapine with paralytic ileus. This patient also did not mention abdominal complaints and/or obstipation. In contrast to our case, there was a longer history of using multiple antipsychotics, and the patient also used risperidone. Simultaneously prescribing medicaments with anticholinergic effects (such as olanzapine, chlorpromazine, amitriptyline, clomipramine, imipramine, nortriptyline) with clozapine should be avoided, because it is likely that this will increase the risk of constipation.[7] Normal serum levels of clozapine do not preclude gastrointestinal complications. The Dutch Clozapine Workgroup Guideline advises to weekly evaluate obstipation by asking the patient for symptoms.[8] However, recent research showed little correlation between reported obstipation and intestinal motility measured by Colon-Transit-Time,[9] possibly because psychotic patients can be insensitive to pain.[10,11] Furthermore, antiserotonergic effects of clozapine may suppress gastrointestinal nociception, which may cause a delay in abdominal symptoms. This often makes the anamnesis unreliable in patients taking clozapine, which could explain the higher mortality rate of acute colonic pseudo-obstruction related to antipsychotics versus other causes.[1,2,12] Because of this mechanism, our patient did not show any discomfort until right before he developed circulatory problems because of outflow restriction of his caval vene due to high abdominal pressure. Our patient also reported passing stool twice, in retrospect his answers were possibly also unreliable because of increasing psychotic disorganization. These findings suggest that relying solely on patient information may not be sufficient. Furthermore, clozapine is a potent α-1 blocker, which causes vasodilation. The effect of epinephrine or norepinephrine is therefore reduced in patients using clozapine, and the effect of epinephrine can be paradoxical, causing refractory hypotension. A positive effect of vasopressin has been described in several case reports.[12–14] In response to the described case, a change in our local hospital guidelines was made regarding the prescription of laxatives for all patients using clozapine. In addition, the clinical pharmacists integrated this guideline in their clinical decision support system, which alerts them when laxatives are lacking in patients using clozapine. Laxatives will be offered as needed to patients starting with clozapine and prescribed daily at a fixed time when the patient uses other anticholinergic medication, including olanzapine, besides clozapine. Increased awareness and a high degree of vigilance in doctors, nurses, patients, and family members are necessary surrounding this topic. We advise to prescribe laxatives prophylactically, to inquire about stool pattern and regularly perform physical examination on patients using clozapine. This advice applies to admitted patients as well as ambulatory patients. Because CIGH occurs in a third of the patients using clozapine, there will be some overtreatment, but adverse events of laxatives are usually mild. Therefore, starting laxatives in all patients outweighs the risk of undertreatment. In case of overtreatment, the use of laxatives can be reduced. Especially in patients experiencing schizophrenia, noncompliance with medication is widespread. Therefore, the use of prophylactic laxatives should still be combined with regular history taking and physical examination. The use of prophylactic laxatives should be the subject of further study.

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AUTHOR DISCLOSURE INFORMATION

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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