DOI: 10.5455/bcp.20110815070819

Antidepressant Drugs and Risk of Venous Thromboembolism: A Case Report and Literature Review

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ABSTRACT:
Antidepressant drugs and risk of venous thromboembolism: a case report and literature review

Venous thromboembolism (VTE), including pulmonary thromboembolism (PTE) and deep venous thrombosis (DVT), is a common disease with a considerably high morbidity and mortality. Mirtazapine, a novel antidepressant with a unique mode of action, is currently widely used in psychiatric practice. Preliminary clinical studies have showed that it is an effective and fast-acting antidepressant with few side effects. Reports about mirtazapine inducing VTE are rare. We present a case of VTE in a woman with depression without any major risk factors for thrombosis where mirtazapine was suspected to be the major associated factor in the development of VTE. In addition, we reviewed the literature to further explore the association between antidepressant drug use and the risk of VTE. As a result, a possible association was indeed found between the two, but no conclusion could be drawn.

Key words: Mirtazapine, antidepressant drugs, pulmonary thromboembolism, deep venous thrombosis, venous thromboembolism, adverse effect.

Bulletin of Clinical Psychopharmacology 2011;21(3):237-41

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Gönderme tarihi / Date of submission: 28 Şubat 2011 / February 28, 2011

Kabul tarihi / Date of acceptance: 15 Ağustos 2011 / August 15, 2011

Bağıntı beyanı:
H.Z., Y.T., Y.Y., Q.Y., X.D., Z.L.: Yazarlar bu makale ile ilgili olarak herhangi bir çıkar çatışması bildirmemişlerdir.

Declaration of interest:
H.Z., Y.T., Y.Y., Q.Y., X.D., Z.L.: The authors reported no conflict of interest related to this article.

INTRODUCTION

Deep venous thrombosis (DVT) and pulmonary thromboembolism (PTE) are distinct but related aspects of the same dynamic disease process known as venous thromboembolism (VTE) (1). VTE is a common disease with an incidence in the United States that exceeds 1 per 1000 and a number of annual new cases exceeding 1,500,000 in European Union countries (1,2). Many risk factors for VTE have been confirmed, such as surgery, fracture, oral contraceptives or estrogen, increasing age and active malignancy (3,4). Beyond that, some studies have reported that there is an association between psychotropic drugs use and occurrence of venous thromboembolism (5-8); however, most of these studies were about antipsychotic drugs and research on antidepressants is rare.

Mirtazapine is a novel antidepressant with a unique mode of action, which can be best summarized as a noradrenaline and specific serotonin antidepressant (NaSSA) (9). Preliminary clinical studies show that it is an effective and fast-acting antidepressant with few side effects that is used widely in psychiatric practice (9). Common side effects of mirtazapine are increased appetite, weight gain, and transient sedation (10). Reports about mirtazapine inducing VTE are uncommon. We present a clinical case report of pulmonary thromboembolism (PTE) and deep venous thrombosis (DVT) in a patient during mirtazapine treatment for depression and also a review the literature to explore the association between antidepressant drug use and the risk of VTE.

CASE REPORT

A 50-year-old woman presented to the emergency department at the West China Hospital of Sichuan University complaining of "left lower extremity swelling for more than twenty days, mild dyspnea for six days and fever for four days". Twenty days ago, the patient found her left lower extremity mildly swollen, which she did not take seriously. In recent days, she experienced mild dyspnea, chest tightness, occasional palpitations and 3 to 4 episodes of syncope. The patient started to suffer from a fever with body temperature around 38°C four days ago.

No chest pain, cough, wheeze, and hemoptysis were reported. The condition worsened and she felt shortness of breath even at rest. She was admitted to the hospital. The patient has had a history of depression for ten years, treated with doxepin 200 mg/day regularly and clonazepam 5mg when needed for insomnia. Her condition had been stable until three months ago when she felt insomnia, depression, and irritability without significant causes. Thinking her depression might have relapsed, she turned to the psychiatrist who recommended she take mirtazapine 30 mg/day, instead of doxepin, and clonazepam 5mg regularly before sleep. The dosage of mirtazapine was gradually increased to 45 mg/day over two weeks. The depressive symptoms were well controlled within three weeks of initiation of mirtazapine. The patient is a housewife, has been postmenopausal for 8 years, always adheres to physical exercise, and is usually physical healthy. She has never taken estrogen and has no history of other substance abuse, surgery, trauma or chronic systemic medical history. There was no family history of VTE. During the treatment with mirtazapine and clonazepam, the patient did not experience significant weight gain or sedation, common side effects of antidepressants.

The physical examination revealed a conscious but mildly dysphoric woman. Her BMI is 23.0 kg/m^2 and the vital signs recorded were blood pressure 115/70 mmHg, heart rate 110 beats/min, respiratory rate 24 breaths/min, and body temperature 38.5°C. The cardiovascular examination disclosed a regular, tachycardic rate without any murmur. Examination of the bilateral chest revealed some moist rales in the right lower lung. There was slight edema in the left lower limb. The rest of the physical examination was negative.

The plasma D-dimer of the patient was 1727.00 μg/L. Blood gas analysis with the patient breathing 35% O_2 through a Venturi mask showed hypoxemia (pO_2 72.0 mmHg, SaO_2 95%). An electrocardiogram suggested sinus tachycardia, right axis deviation and T wave changes. Echocardiography revealed an enlarged right ventricle, tricuspid regurgitation (moderate), pulmonary hypertension (moderate) and foramen ovale separation. Vascular ultrasound revealed left lower extremity deep venous thrombosis. Computed Tomographic Pulmonary Angiography (CTPA) revealed bilateral main pulmonary trunk and lobar pulmonary artery thrombosis, regional consolidation and atelectasis with infection in the right lung (Fig 1). A complete blood count showed mild anemia (hemoglobin 106 g/L), platelet count 85×10^9/L, white blood cell count 14.27×10^9/L. Liver and renal function tests, blood lipid and electrolytes were normal, as were her serial cardiac enzyme levels, autoimmunity and tumor marker tests. A PET-CT scan of the whole body had no positive findings.

Based on the above results, the diagnoses of deep venous thrombosis (DVT) of the left lower extremity and multiple pulmonary thromboemboli (PTE) were established. Soon after that the patient was given thrombolytic therapy with human recombinant tissue-type plasminogen activator (50mg intravenous infusion with micro-pump), anticoagulant therapy with low molecular weight heparin (0.5 ml ih q12h) and warfarin (2.5 mg po qd). At the same time other symptomatic and supportive treatments were given. Due to the suspicion of VTE in the patient associated with the antidepressant mirtazapine, we changed it to citalopram after consulting with the patient's psychiatrist, and left clonazepam unchanged. After these treatments, the patient and her symptoms markedly improved. The D-dimer reduced to 346.00 μg/L and the blood gas analysis was found in the normal range. In addition, echocardiography showed remission of the pulmonary hypertension, and CTPA revealed that the number of pulmonary vessels embolized was significantly reduced. During the whole period of treatment, the depressive symptoms in the patient were well controlled except occasional insomnia. Eventually the patient, who made a good physical and mental recovery, was discharged

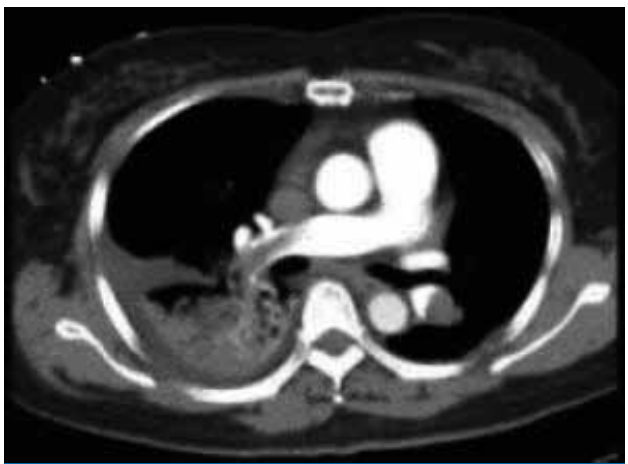

Figure 1: CTPA showing low density over the bilateral main pulmonary artery and lobar pulmonary arteries, the posterior segment of the right upper lobe and the right lower lobe consolidation and atelectasis

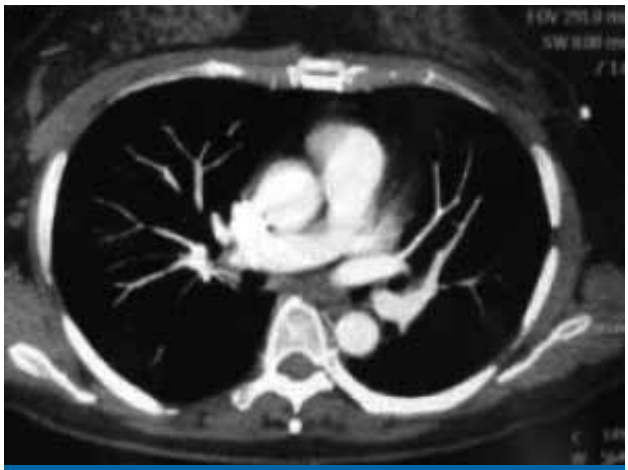

Figure 2: CTPA showing pulmonary arterial thrombi have disappeared completely and the lung inflammation has subsided fully.

after 27 days of inpatient treatment. She continued the anticoagulant therapy with oral warfarin outside the hospital, and after five months of follow-up, she recuperated well (Fig 2).

DISCUSSION

Venous thromboembolism (VTE) is a potentially fatal and not uncommon disease, with many known risk factors. Because the incidence of VTE is gradually increasing in patients with psychiatric disorders (11,12), the association between VTE and psychotropic drugs, mainly including antidepressants and antipsychotics, has been an area for considerable discussion for years.

Many studies have been published about the association between antipsychotic drugs and VTE, and most of them have suggested antipsychotics tend to increase the risk of VTE (5-8,13). However, only limited data are available with regard to antidepressant drug use and the risk of VTE. We performed a literature review of clinical studies relating VTE to antidepressants (Table 1). In all these studies, any other known major risk factors for VTE were well controlled by the analysis. From the table, we could see that the results were inconclusive. Two studies, conducted respectively by Parkin et al. and Jick et al., suggested that there were certain associations between the antidepressant drugs use and VTE (14,17), while in the other four studies no associations were found (6,13,15,16). Most studies only evaluated the effects of all antidepressant use rather than that of an individual antidepressant class or drug. Some studies (6,13), including few subjects with exposure to antidepressants, were conducted primarily to evaluate the association of antipsychotic drug use with risk of VTE, and the evaluation of antidepressant use was secondary. In addition, we also found isolated case reports about antidepressants inducing VTE in the medical literature (Table 2). In all these cases,

Table 1: Clinical Studies on Antidepressants and Venous Thromboembolism (VTE) *

Study	Study Type	Study Population	Sample Size	The Classification of Antidepressants	Results
Zornberg et al (6)	Case control study	Inpatients and Outpatients < 60 years old	Cases n=33, Controls n=156	Not done	Current use: OR =1.7, 95% CI 0.8–3.7, recent use: OR =0.8, 95% CI 0.1–7.4
Thomassen et al (13)	Case control study	Outpatients average age 46.6 years old	Cases n=474, Controls n =474	Not done	OR=2.3, 95% CI 0.6-10.2
Parkin et al (14)	Case control study	Autopsy 15-59 years old	Cases n=62, Controls n=243	Not done	Adjusted OR = 4.9, 95% CI 1.1–22.5
Lacut et al (15)	Case control study	Inpatients and Outpatients < 60 years old	Cases n=135, Controls n=123	Not done	OR = 1.1, 95% CI 0.9–1.5
Ray et al (16)	Retrospective cohort study with control group	Outpatients ≥ 65 years old	Exposed group n=75649, Non-exposed group n=33033	Not done	Adjusted HR=1.02, 95% CI 0.91–1.14
Jick et al (17)	Nested case-control study.	Outpatients ≤ 70 years old	Cases n=782, Controls n=3085	TCA, MAOI, SSRI, NaSSA	All antidepressants: current use OR=1.2, 95% CI 0.9–1.4, recent use OR=1.4, 95% CI 0.9–2.2; TCAs: current use OR=1.4, 95% CI 1.1–1.8, recent use OR=1.3, 95% CI 0.7–2.5; Amitriptyline: OR=1.7, 95% CI 1.2–2.4

*OR: odds ratio; 95% CI: 95% Confidence interval; HR: hazard ratio; current use: receipt of a prescription 1-60 days before the index date; recent use: receipt of a prescription 61-90 or 120 days before the index date; TCA: tricyclic antidepressant; MAOI: monoamine oxidase inhibitor; SSRI: selective serotonin reuptake inhibitor; NaSSA: noradrenaline and specific serotonin antidepressant.

Table 2: Reported Cases of VTE in Patients on Antidepressant Therapy *

Study	Patient	Underlying Condition	Drug Use	Complications	Clinical Outcome
Arnone et al (18)	a 64-year-old woman	Bipolar Disorder	Citalopram	PTE	Recovery
Kurne et al (19)	a 53-year-old man	Depression	Escitalopram	DVT	Unclear
Ginsberg (20)	a 40-year-old man	Schizophrenia and Depression	Mirtazapine and Risperidone	PTE and Rhabdomyolysis	Recovery
DWH Tam (21)	a 48-year-old woman	Depression	Duloxetine and Mirtazapine	PTE	Death

* Citalopram and Escitalopram-selective serotonin reuptake inhibitor (SSRI) class of antidepressant drug; Duloxetine-selective serotonin and norepinephrine reuptake inhibitor(SSNRI) class of antidepressant drug; Risperidone-antipsychotic drug.

the patients didn't have any significant risk factors for thrombosis and the symptoms of deep venous thrombosis (DVT) or pulmonary thromboembolism (PTE) showed up within four months of starting antidepressant use, so the antidepressants were considered to be one of the major contributing factors in the development of VTE.

Our case was a 51-year-old woman who had had depression for ten years. After taking mirtazapine more than 2 months, she began experiencing the symptoms mentioned previously. The patient was confirmed to have DVT and PTE through a series of examinations. The laboratory tests found no clues of malignancy and autoimmune diseases, and there was no significant weight gain or sedation in the patient caused by antidepressant therapy. Mirtazapine treatment and the appearance of VTE in the absence of any other major risk factors drew our attention to a possible association between mirtazapine and this particular adverse event. Clonazepam, which was combined with mirtazapine to improve sleep of the patient, may be another contributing factor; however, although exacerbation of phlebitis associated with oral diazepam use has been reported (22), no such relation has been reported for clonazepam, a benzodiazepine with different pharmacological properties. Furthermore, the fact that the patient had been taking clonazepam for several years without any adverse reactions also decreases the likelihood of this possibility. For these reasons, we believe that it is very likely that mirtazapine caused the DVT in our patient and ultimately led to her PTE.

Even though the underlying mechanisms explaining the association between antidepressant drugs and VTE are unknown, several hypotheses and explanations have been proposed. One explanation is that antidepressant drugs may induce weight gain (9), and obesity is one of the risk factors for VTE (4). Secondly, venous stasis exacerbated by sedation, commonly found in patients treated with antidepressant drugs, may contribute to the processes that increase the risk of thrombosis. Above are some speculations of indirect effects of antidepressant drugs, yet the patient we presented did not experience obvious weight gain or sedation. Some other researchers inferred that there may be more important and direct mechanisms (19,23). It has been shown that antidepressants, especially selective serotonin reuptake inhibitors (SSRIs), not only affect neuronal serotonin (5-HT) uptake, but additionally modulate peripheral serotonin, resulting in an increase in serotonin near specific serotonin receptor subtypes in discrete regions of the body where relevant physiological processes are regulated. Serotonin itself is a platelet agonist, and in the presence of other proaggregatory factors (e.g., adenosine diphosphate, adrenaline, collagen), it significantly potentiates the aggregation of platelets (24). Consequently, the rise in serotonin levels may lead to an increase in the risk of hypercoagulability. Mirtazapine, as an antagonist of α_2-adrenergic receptors, histamine H_1, 5 - HT_2 and 5 - HT_3 receptors (10), may also increase the release of serotonin, resulting in a rise in the serotonin levels of the blood. On the other hand, citalopram, also an SSRI antidepressant drug, which was used as an alternative to mirtazapine after the occurrence of VTE in our patient, may also cause VTE according to the literature and possible mechanisms mentioned above. In order to answer this question, further follow-up is needed to observe if any new VTE occurs in our patient. The mechanisms causing such an adverse effect, directly or indirectly, including whether there were any drug interactions remain to be further studied.

We hope that this case report and the review of relevant literature will alert clinicians to this potential fatal adverse effect of mirtazapine and other antidepressants. When treating patients with these drugs, clinicians must pay special attention to possible signs and symptoms of VTE, since early diagnosis and prompt treatment can improve the outcome. In addition, more laboratory and clinical studies are needed in order to further elucidate the association between antidepressant drugs and VTE and explore the possible mechanisms causing this adverse effect.

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