Pulmonary embolism in a patient receiving risperidone and paliperidone: A case report and review of the literature

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ABSTRACT

Several cases of pulmonary embolism (PE) have been associated with antipsychotic treatment. We report a case of an otherwise healthy 27-year old male who developed a PE after receiving paliperidone long acting injection. The patient received risperidone long acting injection for over 3 months before initiating paliperidone, but was switched incorrectly. After 3 weeks on paliperidone long acting injection the patient developed a PE requiring hospitalization and a course of anticoagulation. A review of atypical antipsychotic-induced venous thromboembolism is discussed.

KEYWORDS

pulmonary embolism, atypical antipsychotic, venous thromboembolism, paliperidone, risperidone

INTRODUCTION

Bipolar I disorder is a mood disorder involving major depressive and manic episodes.[1] Paliperidone is an atypical antipsychotic that can be used in the treatment of manic or mixed phases of bipolar disorder. Paliperidone long-acting injection (PLAI) is a depot injection of the major active metabolite of risperidone which is administered by giving two injections one week apart, and then monthly therafter.[2] A long-acting injection is beneficial for patients that may not reach remission due to poor persistence.

Pulmonary embolism (PE) is a type of venous thromboembolism (VTE) that is potentially fatal if left untreated. A PE is a rare, but serious, side effect linked to the use of antipsychotics; antipsychotic use is a drug-induced risk factor because it may induce pathological blood clotting in patients.[2,3] PE's were not reported during the clinical trials of risperidone or paliperidone; only in post-marketing case reports of risperidone has this potentially fatal side effect been realized.

We report a case of PE potentially related to PLAI use in a patient with bipolar disorder who recovered without complication.

CASE REPORT

A 27 year old Caucasian male with a history of substance abuse and bipolar I disorder was admitted to a psychiatric hospital after numerous complaints of paranoia, hallucinations, disorganization, and suicidal and homicidal ideation. Upon admission, the patient was administered a urinary drug screen which tested negative for recent cocaine use. The patient's mood was depressed, but he had a significant history of mania with psychosis in the past. He was started on oral risperidone and titrated up to 3 mg twice daily. Then, he received a risperidone long-acting injection (RLAI) 25 mg intramuscularly a few days later; he was continually supplemented with oral medication. Throughout hospitalization, the patient's mood stabilized and he denied any symptoms of psychosis or suicidal thoughts at discharge. His discharge medication regimen was risperidone orally dissolvable tablets 2 mg twice daily, and was scheduled for a RLAI 25 mg injection two weeks after the first injection was given. He received RLAI 25 mg every two weeks for three and a half months without oral supplementation. The patient no longer wanted to come to the clinic every two weeks to receive his injection so he was switched to PLAI. He received a dose of 234 mg when his next RLAI was due and one week later received 156 mg.

Three weeks after beginning PLAI, the patient presented to the hospital after 2 days of acute onset pleuritic chest pain and dyspnea. He was not currently taking any other medications and did not have any current medical conditions, but admitted to using cocaine a few days

before his hospitalization. Upon admission, the patient underwent a CT angiogram (CTA) of the chest, chest X-ray, complete metabolic panel, complete blood count with differential, and coagulation panel. Results showed a left posterior basal segmental pulmonary thromboembolism with the chest CTA, an elevated d-dimer of 1.2 mg/L, and a low INR of 0.83. He was treated initially with enoxaparin 80 mg SQ twice daily and warfarin 5 mg daily. Two days later his INR was 1.25 and was given warfarin 7.5 mg. On the third day, his dyspnea remained stable, his INR was 1.64, and he was given warfarin 10 mg. On day four of hospitalization, his lungs were clear to auscultation bilaterally and his INR was 2.15. He was discharged from the hospital on warfarin 7.5 mg daily and told not to continue his PLAI. When he followed up at the outpatient psychiatry clinic after hospital discharge, the patient's PLAI was discontinued. He was switched to fluphenazine four weeks after stopping PLAI in preparation for another long acting injection. A Naranjo scale was calculated and the PE was determined to be probably related to the PLAI.[4]

DISCUSSION

Patients with psychiatric illness may have an increased risk for VTE and antipsychotics may further increase this risk.[5] Of note, the patient's cocaine use can be ruled out as a primary cause of his PE. While intravenous cocaine use has been previously shown to result in embolisms,[6] the patient's primary method of use was nasal inhalation; there has been no evidence supporting a link to PE.[7-9]

In addition to risperidone, other atypical antipsychotics such as amisulpride,[10] clozapine,[11-12] olanzapine,[13-16] and sertindole[17] have also been associated with DVT or PE. Clozapine is the most common atypical antipsychotic that has been associated with thromboembolism; this is thought to be due to the strong affinity to serotonin, histamine and alpha-adrenergic receptors.[15] Secondarily, olanzapine has numerous reports of this phenomenon, most likely because of the close correlation between the two chemical structures.[18-19] Although amisulpride and sertindole are not available in the United States, they also have suspected and documented links to thrombus formation. Refer to Table 1 for a thorough review of the case reports.

Risperidone has a high affinity for 5-HT_{2A} receptors which may increase clotting – through serotonin-induced platelet aggregation – thus increasing the risk of thrombosis.[20] Additionally, paliperidone has the same proposed mechanism of action as its parent drug: serotonin 5-HT_{2A} and dopamine D_2 antagonism.[2]

Though no other published reports could be identified with paliperidone, several cases have been reported with risperidone. A retrospective chart review searched reports of patients from an emergency department who presented with pulmonary thromboembolism associated with antipsychotic use over a 5-year period. No patient was immobile, but in all cases, PE occurred early in the morning, within hours of waking. Seven cases were identified. Two female patients were found to be receiving risperidone; the other five cases both males and females taking chlorpromazine, levomepromazine, and propericiazine. One patient took risperidone for 6 days and died from a massive thrombus in the lumen of the main branches of the bilateral pulmonary arteries. The other patient took risperidone for 40 days and survived with successful treatment, but developed anoxic encephalopathy.[21] Another report describes the development of a PE occurring three separate times in a male patient using olanzapine then risperidone. The patient developed a PE after using olanzapine for 12 weeks and the medication was discontinued. He was initiated on risperidone at this time. Three weeks later, another PE had developed which may have been due to nonadherence to anticoagulation therapy. A chest X-ray showed multiple peripheral pulmonary emboli. Risperidone was continued along with close supervision to adhere to anticoagulation. Sixteen weeks later, a third incidence occurred and a chest CT scan and Doppler ultrasound demonstrated bilateral PE. The patient was dyspneic in each instance, along with having an elevated d-dimer. After investigating potential factors, the most probable cause of the PE was associated with antipsychotic use.[13] A case series describes three elderly females and one elderly male presenting with either unilateral or bilateral PE by CT of the chest ranging from 2 days to 4 weeks of starting risperidone. All four patients stabilized with treatment and recovered before hospital discharge.[22] In all the cases described here, the patients had no family history of emboli, had a normal BMI, and ages ranged from early 20s to late 80s.

CONCLUSION

The case reported here shows similar characteristics to the cases reviewed above utilizing the use of risperidone. The patient developed his PE three weeks after beginning paliperidone, which is congruent to the development of a PE after starting antipsychotic treatment. It is noteworthy that risperidone was likely at steady state as the patient had been receiving it for approximately 16 weeks before the transition to paliperidone. Additionally, the PLAI was initiated incorrectly. When switching from another long

Table 1. Case reports of second generation antipsychotic-associated thromboembolism

Second Generation Antipsychotic	Associated VTE	Dose	Duration Before VTE	Outcome/Result
Case Reports				
Amisulpride[10]	PE	400 mg/day	5 months, but had been discontinued for 1 month	Received heparin and antibiotics for 3 days, followed by acenocoumarol for 6 months. Patient made a full recovery.
Clozapine[11]	PE	100 mg/day	2 months	Patient's family denied tissue plasminogen activator (TPA) and patient died despite resuscitative efforts.
Clozapine[12]	DVT	150 mg twice daily	15 days	Patient received heparin, enoxaparin, and warfarin, and made a full recovery.
Olanzapine[13]	DVT	20 mg/day	12 weeks	After DVT, olanzapine was discontinued and warfarin was maintained for 6 months. Twelve weeks without therapy, patient began having psychotic symptoms, and risperidone was started. Patient developed two more VTEs; risperidone treatment is discussed in the text.
Olanzapine[14]	PE	?	~2 days after overdose	Patient stored 90 tablets and took these with a clear suicidal intent. Following medical treatment with anticoagulation and antibiotics, patient made a full recovery.
Olanzapine[15]	PE	?	?	Patient was found dead in her apartment. An autopsy examination was remarkable for an acute PE and an adherent thrombus within the left popliteal vein after dissection of the leg vessels.
Olanzapine[16]	DVT and suspected PE	5 mg/day	39 days	Phlebography revealed a DVT and a PE was suspected but not confirmed by imaging techniques. Patient received warfarin and continued olanzapine. Four months into olanzapine treatment, patient died of suspected COPD and dementia.
	DVT	5 mg/day	42 days	Patient was treated with warfarin and was started on risperidone. Patient made a full recovery and had no subsequent VTE.
	DVT followed by suspected PE	5 mg/day	DVT after 11 days. PE after another 3 days	Patient received warfarin after DVT diagnosis. After general condition deteriorated and developed a PE, heparin was added. Condition continued to deteriorate and patient died the next day. Patient was also taking tamoxifen for breast cancer treatment.
Sertindole[17]	DVT	4 mg/day titrated up to 16 mg/day within 9 days	11 days	Received short-term heparin followed by warfarin. At one-month follow-up, patient had made a full recovery.
Case Series				
Clozapine[23]	VTE	375 cases reported		
Clozapine-Quetiapine[24]	VTE	<11 cases reported		
Clozapine[25]	PE	6 cases reported from an autopsy series		
Olanzapine[23]	VTE	91 cases reported		
Olanzapine[24]	VTE	15 cases reported		
Olanzapine[25]	PE	9 cases reported from an autopsy series		
Sertindole[23]	VTE	9 cases reported		

acting injection at steady state, the loading dose is not needed. PLAI should be administered in place of the previous long acting injection and then dosed monthly. This rapid increase in the dose may have contributed to the development of the patient's PE. Further investigation into this phenomenon is needed to

determine a clinically significant correlation of paliperidone, risperidone, and PE. There are growing reports of antipsychotic-induced VTEs, and this is a clinically significant occurrence. Although the data show it is most common in typical antipsychotics, atypical antipsychotics, including clozapine, olanzapine, and risperidone, are becoming common causes of thrombus and embolus formation.

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How to cite this editor-reviewed article
Casey A, Saitz M, Swaim PR. Pulmonary embolism in a patient receiving risperidone and paliperidone: A case report and review of the literature. Ment Health Clin [Internet]. 2013;3(3):144-7. Available from: http://dx.doi.org/10.9740/mhc.n166827