

## CAZURI CLINICE

# Acute massive pulmonary embolism associated with olanzapine therapy and no significant personal history in a young male - case report and literature review

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### REZUMAT

**Embolie pulmonară masivă asociată tratamentului cu olanzapină și fără antecedente semnificative la un adult tânăr**

Autorii prezintă un caz de tromboembolism pulmonar (TEP) masiv asociat cu pleurezie stângă la un bărbat tânăr, în vârstă de 28 de ani, nefumător, în tratament cu olanzapină 10 mg/zi în ultimele 4 luni. Sistarea tratamentului anti-psihotic, asociată cu terapia antitrombotică au indus remiterea TEP. În literatura de specialitate, asemenea complicații trombotice au fost semnalate în asociere cu diferite substanțe anti-psihotice, dar incidența, factorii favorizanți adjuvanți, mecanismele biologice incriminate rămân un subiect de dezbătut atât în sfera cardiopulmonară, cât și psihiatrică.

**Cuvinte-cheie:** tromboembolism pulmonar, anti-psihotice, olanzapină

### ABSTRACT

We report the case of a 28 years old, non-smoker male with a massive pulmonary embolism and left pleural effusion associated and probably induced by olanzapine 10 mg once daily in the previous 4 months, completely recovered after 18 days of stopping the anti-psychotic and thrombolytic treatment. Thrombotic events have been reported with the use of anti-psychotic compounds, although the incidence, predisposing factors, and biological mechanisms associated with these events in psychiatric patients are subject to debate.

**Keywords:** Pulmonary embolism, anti-psychotics, olanzapine

### Introduction

Pulmonary embolism is a potentially lethal condition. Acute massive pulmonary embolism (PE) accounts for approximately 50,000 deaths per year in the United States<sup>(1)</sup>. The first main symptoms are dyspnea and chest pain and signs as tachycardia and tachypnea, especially in patients with heart disease. There are a few published reports in young apparent healthy men, although the incidence of PE with documented deep vein thrombosis were reported even in children. Less clear is the relationship between olanzapine therapy and massive PE.

### Case report

We report the case of acute massive pulmonary embolism associated with the atypical anti-psychotic, olanzapine, in a 28 years aged young male. Four months prior to hospital admission, he had been started on olanzapine therapy for a bipolar psychic disorder.

The patient was admitted in the department with fever, left-sided pleural chest pain and shortness of breath. His past medical history was significant only for bipolar disorder, diagnosed by a psychiatrist 9 months prior to his presentation, and for which olanzapine (Zyprexa) 10 mg once daily was prescribed. He also received clonazepam (2mg/day) and acid

valproic (500 mg/day). He had no personal history or family history of thrombosis. He denied recent trauma or surgery, long-haul travel, weight loss. He also denied taking over-the-counter products or dietary supplements. He had never smoked, did not use alcohol or illicit drugs. Physical examination showed: fever (37,8° C), cyanosis, severe dyspnea, tachycardia 130/min, blood pressure 100/60 mmHg, right ventricular gallop rhythm, dullness with no respiratory rales in the left lower thorax, dilated jugular veins, mild decreased oxygen saturation Sa O<sub>2</sub> of 90%.

Blood tests showed inflammation, (erythrocyte sedimentation rate - 45 mm/1h, fibrinogen 807 mg/dL), increased white blood cell count of 17,500/mm<sup>3</sup> and a high rate of neutrophils (13,100/mm<sup>3</sup>), D Dimer >5 mcg/mL (normal value <0.7 mcg/mL), increased creatin-kinase at 275 UM (normal values range: 24 - 200 UM), LDH - 743 U/L (normal values range: 240 - 480 U/L), hypercholesterolemia, hypertriglyceridemia.

Chest X-Ray showed mild intensity, ill-defined, homogenous opacity in the middle left lung associated with a minimal left pleural effusion (figure 1).

The electrocardiogram (ECG) performed on 26 May 2008 revealed: sinus tachycardia 130/min, QRS Axis +30°, S1 Q3

**Figure 1. Chest X-ray on admittance day: mild intensity, ill-defined, homogenous opacity in the middle left lung associated with a minimal left pleural effusion**



**Figure 2. Heart ultrasound reveals a dilated right ventricle with change of the left ventricle geometry and paradoxical movement, inferior vena cava dilated without colaps, bifid pulmonary flow, a mobile, moderately echogenic formation in the left pulmonary artery - thrombus**



T3; on the admission day - 30 May: sinus tachycardia 150/min, QRS Axis +90°, incomplete right bundle branch block, ST elevation 0.5 mm in V1,V2 with negative T waves in V1, V2, SIQ3T3.

Considering the clinical context, the ECG changes and elevated D-dimer level, PE was suspected, the patient having an emergency ultrasound. Cardiac ultrasound (figure 2) reveals a dilated right ventricle and modified geometry of left ventricle, flattened interventricular septum with paradoxical movement. In the left pulmonary artery and intermittently in the main pulmonary artery it showed the presence of a mobile, echogenic formation - a thrombus. At the superficial femoral vein (dilated, incompressible) there is also a suspected clot.

Due to the poor general and cardiovascular status the emergency treatment decision was promptly implemented on the above data and thrombolytic treatment was started without expecting further imagistic data, using the classical streptokinase protocol (250,000 U.I. in 150 ml 5% D/W in 30 min,

**Figure 3. CT of the thorax showing remnant left pulmonary artery embolus (0.7 cm) and left lower lobar branch pulmonary infarction and minimal left pleurisy**



**Figure 4. CT of the thorax showing well circumscribed consolidation in the middle area of the left lung. The opacification is not strictly segmental**



followed by 100,000 U.I./h for the next 24 hours). Fibrinogen and coagulation tests monitored the lytic state within accepted limits (fibrinogen >100 mg/dl and aPTT 45-80 sec.), and progressive clinical improvement was noted, including the disappearance of cyanosis and clinical signs of right ventricular failure.

Unfractionated heparin infusion was started following the thrombolytic therapy (1500 IU/h, aPTT 1.5-2 times the normal values) for the first 48 hours, followed by enoxaparin 2x1 mg/kg s.c. for the next 7 days, while oral anticoagulant (acenocumarol) was introduced and titrated to efficiency. Fever and evidence of a persistent left lung opacity determined antibiotic treatment (ampicilin-sulbactam 4 g/day) for 14 days.

A chest CT scan was performed on the 14th day, revealing remnant left pulmonary artery embolus (0.7 cm) and left lower

lobar branch, pulmonary infarction, a minimal left pleurisy (figure 3) and a well circumscribed consolidation in the middle area of the left lung (figure 4).

A hipercoagulability panel, which included the presence of factor V Leiden, the G20210A prothrombin gene mutation, homocysteine level, anticardiolipin antibodies and level of protein C, S, and anti-thrombin, was negative. Given the existence of prior reports linking atypical antipsychotic agents with elevated prolactin levels and PE2, prolactin level was measured. The level was normal 10,4 ng/mL (N = 2,6-13,1ng/mL).

Based of the suspicion that olanzapine could have been involved in inducing PE in this patient, we discontinued this antipsychotic and his medication changed to Amisulprid (Solian) 200mg/day and Trazodonum (Trittico) 150 mg/day.

He remained hospitalized and his further course was favorable; he was confined in bed in intensive care unit for 3 days. Later, in the 5th day, he was moved from the ICU in the general cardiology ward. The pulmonary pressure estimated by ultrasound examination decreased, the ECG remained stable and he was discharged the 18th day on oral anticoagulant therapy, and on the above mentioned psychiatric drugs - which he did not take. He was followed-up weekly in the first month, every 2 weeks in the second month and monthly afterwards. An episode of mild hemoptysis, with no elements of a new thromboembolic phenomenon, was attributed to an anticoagulant overdose. He repeated a psychotic episode 7 month later- during which a psychiatric tentative of olanzapine reintroduction was strongly discouraged by the consulting cardiologist and pulmonologist.

### Discussion

Olanzapine, an antipsychotic and neuroleptic, is used to treat psychotic disorders. As an adverse event, neuroleptic malignant syndrome is a rare but life-threatening effect. Other adverse effects are orthostatic hypotension, tachycardia, chest pain, blurred vision, dry mouth, nausea, vomiting, anorexia, constipation, abdominal pain, weight gain, urinary retention, urinary frequency, enuresis, impotence, amenorrhea, gynecomastia, breast engorgement, premenstrual syndrome, rash, dyspnea, rhinitis, cough, pharyngitis, extrapyramidal symptoms, seizures, headache, fever, insomnia, somnolence, agitation, nervousness, hostility, dizziness, hypertonia, tremor, euphoria, joint pain, and twitching. Thrombotic events have been reported with the use of antipsychotic compounds, although the incidence, predisposing factors, and biological mechanisms associated with these events in psychiatric patients are subject to debate<sup>(3-10)</sup>. As for the other atypical antipsychotics, the "Adverse Reactions" section lists pulmonary embolism/embolus for risperidone and olanzapine, deep thrombophlebitis for quetiapine, and pulmonary embolus and deep thrombophlebitis for ziprasidone<sup>(11)</sup>. Low-potency antipsychotic drugs were more strongly associated with venous thrombosis than high-potency drugs<sup>(12)</sup>.

The risk for venous thrombo-embolism (VTE) seems to be highest during the initial months of treatment with antipsychotics<sup>(12)</sup>. The biological mechanisms responsible for this possible adverse drug reaction are unknown, but a number of hypotheses have been suggested. The increased risk may be the result of drug-induced sedation, obesity, hyperleptinaemia, antiphospholipid antibodies and increased activity in the coagulation system<sup>(12)</sup>. The association could also be related

to underlying risk factors present in patients with psychosis such as smoking<sup>(12)</sup>, but our case was a never smoker. Other factors that may have contributed to this patient's PE: overweight (body mass index >29,5), absence of physical activity.

A study, published in 2007, revealed Clozapine as the only compound that increased platelet adhesion and aggregation and shortened APTT. The effect appeared at therapeutic concentrations and was significant but weak<sup>(13)</sup>.

Risperidone and 9-OH-risperidone reduced epinephrine- and 5-HT-induced human platelet aggregation but did not significantly alter other measures of platelet function, plasma coagulation, or fibrinolysis in vitro<sup>(14)</sup>.

### Conclusion

Despite the limitations of present knowledge, chest clinicians should be aware of this possible adverse drug reaction and should consider interrupting or changing the antipsychotic regimen in patients in whom this reaction is suspected. Patients who have had one episode of VTE during antipsychotic therapy related with an affinity for 5HT<sub>2</sub> receptors should receive neuroleptics from other classes, such as amisulpride, which does not interact with 5HT<sub>2</sub> receptors<sup>(15)</sup>. They should also be closely monitored to ensure early detection and prompt treatment of VTE. More studies are needed in order to further elucidate this adverse effect, particularly to determine the incidence rate, possible predisposing factors and the biological mechanisms involved.

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