中文題目：Paliperidone 導致的慢性血栓栓塞性肺動脈高壓：病例報告

英文題目：Paliperidone-Induced Chronic Thromboembolic Pulmonary Hypertension: A Case Report

作　　者：張雋威[1], 林奕瑱[2], 陳志維[3], 陳必立[2], 高永達[3], 黃群耀[1,3]

服務單位：[1]臺北醫學大學附設醫院內科部, [2]臺北醫學大學附設醫院藥劑部, [3]臺北醫學大學附設醫院心臟內科

Abstract:

Chronic thromboembolic pulmonary hypertension (CTEPH) is an uncommon but disabling disease that causes chronic pulmonary hypertension, mainly due to diffuse pulmonary artery thromboembolisms. Antipsychotic drugs are known to increase the risk of pulmonary embolisms. However, to our knowledge, there is no report that suggests antipsychotic drugs are a contributing factor in CTEPH. We herein report a case of CTEPH with progressive pulmonary hypertension and right heart failure after the use of an antipsychotic drug, paliperidone. Medical treatment with riociguat and anticoagulant is beneficial for inoperable or persistent CTEPH. Patient underwent percutaneous balloon pulmonary angioplasty (BPA) successfully.

Case report:

A 62-year-old female without significant medical illness had been diagnosed with schizoaffective disorder since 2011. She was initially treated with risperidone. Her treatment was switched to paliperidone at a dose of 3 mg/day in June 2014 due to persistent hallucinations. She visited a cardiology clinic for shortness of breath in February 2016. A pulmonary function test did not show any obstructive lung disease. An echocardiogram revealed preserved left ventricular systolic and diastolic function but a peak tricuspid regurgitation velocity of 3.2 m/sec. No valvular heart disease was noted. However, the peak tricuspid regurgitation velocity progressively increased to 5.2 m/sec within a year, accompanied by a D-shaped left ventricle (eccentric index 1.2), severe right ventricular dilatation and dysfunction, right atrial dilatation, and a NT-proBNP of 2930 pg/mL. Chest computed tomography showed engorged pulmonary arteries with small, suspicious thrombi in the distal segments. No emphysema or interstitial lung disease was noted. The patient was then admitted to the hospital for hemoptysis, lower extremity edema, and progressive dyspnea. Her room air oxygen saturation was 80%. A lung perfusion scan showed multiple mismatched perfusion defects in bilateral lung fields, which demonstrated a high probability of CTEPH. The patient underwent a right heart catheterization that demonstrated an elevated mean pulmonary arterial pressure of 74 mmHg, a pulmonary capillary wedge pressure of 14 mmHg and a cardiac index of 2.7

L/min/m2 (reference range 2.5-5 L/min/m2 ). A 6-minute-walk distance test was performed with a result of 129 meters. Blood analysis showed a normal coagulation profile. She had no other known risk factors for venous thromboembolisms except the use of paliperidone. Paliperidone was discontinued and changed to aripiprazole. Since her CTEPH involved the distal segments of the pulmonary arteries and she refused pulmonary endarterectomy, she was started on riociguat and rivaroxaban . Three months later, her dyspnea and lower extremity edema were resolved. Her oxygen saturation on room air was improved to 92%. The 6-minute-walk distance had increased to 300 meters. The peak tricuspid regurgitation velocity was decreased to 4.6 m/sec. Percutaneous balloon pulmonary angioplasty (BPA) was performed on September 2019 for dyspnea on exertion.

Discussion:

CTEPH is an uncommon condition that may occurs after overt pulmonary embolism, typically followed by a honeymoon period.[1] During the honeymoon period, symptoms usually are absent despite the onset of pulmonary hypertension.[1] Therefore, CTEPH is oftentimes not detected until pulmonary hypertension worsens and causes dyspnea, hypoxemia, and right ventricular dysfunction.[1] The risk of the development of CTEPH is increased in patients with chronic inflammatory disorders, cancer, and coagulopathy.[1] In the present case, patient had no known risk factors for CTEPH.

To our knowledge, this is the first case report indicating possible relation between antipsychotic drugs and CTEPH. As thrombosis is the triggering factor of the development of CTEPH, antipsychotic drugs have been associated with increased risk of venous thromboembolism.[2] In addition, nitric oxide may play an important role in the pathophysiology of CTEPH as reduced endogenous nitric oxide levels were found in patients with CTEPH.[1] Studies have suggested that antipsychotic drugs may affect plasma nitrates level and decrease expression of endothelial nitric oxide synthase.[3, 4] Antipsychotics drugs may facilitate the development of CTEPH by altering nitric oxide availability in pulmonary vascular endothelium.

While most of the antipsychotics are associated with increased risk of pulmonary embolism, a retrospective analysis showed that quetiapine and aripiprazole were not significantly correlated with increased risk of pulmonary embolism.[2] In the present case, paliperidone was discontinued after the diagnosis of CTEPH and changed to aripiprazole. Drug treatment with riociguat is beneficial and recommended by the guideline for inoperable CTEPH patients. Further treatment of BPA led to significant

improvement in New York Heart Association functional class and the 6-minute walking distance.[5]

In conclusion, the present case observed a progressive pulmonary hypertension during the use of paliperidone. This case report suggests that antipsychotics may be a contributing factor of the development of CTEPH.

References

1. Simonneau G, Torbicki A, Dorfmuller P, Kim N. The pathophysiology of chronic thromboembolic pulmonary hypertension. Eur Respir Rev. 2017;26.
2. Allenet B, Schmidlin S, Genty C, Bosson JL. Antipsychotic drugs and risk of pulmonary embolism. Pharmacoepidemiol Drug Saf. 2012;21:42-48.
3. Minutolo G, Petralia A, Dipasquale S, Aguglia E. Nitric oxide in patients with schizophrenia: the relationship with the severity of illness and the antipsychotic treatment. Expert Opin Pharmacother. 2012;13:1989-1997.
4. Zhang XR, Zhang ZJ, Jenkins TA, Cheng WR, Reynolds GP. The effect of chronic antipsychotic drug administration on nitric oxide synthase activity and gene expression in rat penile tissues. Eur Neuropsychopharmacol. 2010;20:211-217.
5. Wang W, Wen L, Song Z, Shi W, Wang K, Huang W. Balloon pulmonary angioplasty vs riociguat in patients with inoperable chronic thromboembolic pulmonary hypertension: A systematic review and meta-analysis. *Clin Cardiol*. 2019;42(8):741–752. doi:10.1002/clc.23212