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Title Page

Emergence of Neuroleptic Malignant Syndrome While Switching Between Risperidone and Paliperidone

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*Manuscript

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***To the Editor**:*

Paliperidone, an active metabolite of risperidone, is a novel second-generation antipsychotic drug with favorable pharmacokinetic properties and safety profiles.[1] Nevertheless, the risks of severe adverse effects, such as neuroleptic malignant syndrome (NMS), remains a threat in patients receiving paliperidone. To date, there have been two case reports addressing NMS induced by paliperidone.[2,3] Strategies regarding shift medication to paliperidone should keep alert about this risk. We herein report a patient who developed full-blown NMS when the regimen was switched between risperidone and paliperidone. This adverse event has been reported to the National Reporting Center of Adverse Drug Reactions in Taiwan.

CASE REPORT

"Mr. A," a 32-year-old man, had suffered from chronic schizoaffective disorder for more than four years. The main clinical manifestations included catatonia and depressed mood. He had no history of substance abuse. During the most recent two years, he had been stabilized by treatment with risperidone 4 mg/day, venlafaxine 150 mg/day, and lithium 300 mg/day. Due to his chronic hepatitis, risperidone was shifted abruptly to paliperidone, which was started at 3 mg/day. Meanwhile, venlafaxine, lithium and benztropine remained the same.

Three weeks later, he displayed negativism, mutism, and slight muscle rigidity. His family brought him to the outpatient clinic four weeks after the initiation of paliperidone. Under the impression of exacerbated catatonia, the regimen was

changed back to risperidone 4 mg/day, but he complained of increased stiffness and difficulty in swallowing. Gradually, he became incontinent, agitated and finally delirious at home. He was sent to the emergency room six days later with severe muscle rigidity, tremor, heavy perspiration and confused consciousness. Physical examination revealed tachycardia (125 bpm), hypertension (154/113 mmHg), and increased body temperature (38.2℃). Laboratory tests showed an elevated creatine kinase (CPK) level of 1210 U/liter (normal 14-170 U/liter) with leukocytosis (WBC count, 12300). Within 12 hours, his blood pressure soared to 190/133 mmHg and dyspnea was evident. The serum WBC count increased to 17700 and serum myoglobulin concentration rose to 159.3 ng/ml (normal 17.4-105.7 ng/ml). NMS was diagnosed and the patient was admitted to the intensive care unit immediately. That night, he underwent intubation because of respiratory failure.

During hospitalization, a series of examinations excluded the diagnoses of CNS infection, endocrine problems, and other drug-related toxic effects. In addition to supportive treatment, diazepam (for muscle relaxation) and dopaminergic agonists (bromocriptine and amantadine) were also given. Nevertheless, severe rigidity, elevated CPK and body temperature still persisted. Dantrolene was administered. Gradually, his CPK level dropped into the normal range and he was discharged 3 weeks after admission.

During outpatient treatment, the persistence of psychotic symptoms such as negativism and mutism led us to use aripiprazole starting at 2.5 mg/day. The patient's mental status gradually improved under treatment with aripiprazole 5 mg/day and venlafaxine 150 mg/day, and no signs of NMS or extrapyramidal side effects were observed.

DISCUSSION

The patient met the DSM-IV-TR research criteria for NMS.[4] The switch from 4

mg/day of risperidone to 3 mg/day of paliperidone would reduce brain concentrations of paliperidone.[5] The patient had a relapse of his catatonic condition on a lower dose of antipsychotic. Full-blown NMS developed from the catatonic state after risperidone was reinstated. The temporal sequence of the four predominant signs of NMS is mental status changes, rigidity, hyperthermia, and autonomic dysfunction in most cases.[6] The rigidity and mental status change, the common phenomena of catatonic symptoms and the initial signs of NMS presented in this case posed a diagnostic dilemma. In patients undergoing such a switch in antipsychotics, clinicians should carefully evaluate any features suggesting NMS and should not rule out the possibility of NMS when severe rigidity, hyperthermia or autonomic instability are not initially apparent.[7]

The proposed dosing of paliperidone when switched from risperidone is still to be tested. In this case, we are not certain if the relapse of catatonic symptoms could be prevented when paliperidone was initiated at a higher dose. However, the re-exposure to risperidone at a higher equivalent dose (compared to 3 mg/day of paliperidone) converted the catatonic state to NMS. From this case experience, the switch of risperidone to paliperidone should be started with an adequate dose. Furthermore, if patients are not tolerant of paliperidone, the clinician should be vigilant to the emergence of adverse events during the process of switching back to risperidone.

Patients with catatonic symptoms are at higher risk of NMS during anti-dopaminergic treatment.[8] Furthermore, the differential diagnosis between catatonic symptoms and NMS is problematic. In case of doubt, the diagnosis of NMS should be postulated for obvious reasons. Clinicians should balance between the risk of NMS and the benefits of antipsychotics in such patients.

In terms of the use of antipsychotics following NMS, restarting antipsychotic treatment has been associated with a frequency of developing NMS again as high as

30%.[9,10] Aripiprazole was chosen in this case with a satisfactory result, implying that patients requiring antipsychotic treatment can be successfully treated provided precautions are taken in terms of starting at a low dose, monitoring for early signs of NMS and continually balancing the benefits and risks of further antipsychotic use.[8]

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