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Withdrawal seizure associated with high dosage of aripiprazole and fluoxetine: a case report

Jian-An Su[1,2,3*], Shih-Yong Chou[1,2,3], Ching-Shu Tsai[1,2,3], Tai-Hsin Hung[1,2,3]

[1]Department of Psychiatry, Chang Gung Memorial Hospital, Chiayi, Chinese Taipei;
[2]Graduate Institute of Clinical Medical Sciences at Chang Gung University, Taoyuan, Chinese Taipei;
[3]Department of Nursing, Chang Gung Institute of Technology, Taoyuan, Chinese Taipei.
E-mail: *sujian@adm.cgmh.org.tw

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ABSTRACT

Aripiprazole, a third-generation antipsychotic, has been considered to have a high safety profile and rare withdrawal symptoms. We reported the case of a schizophrenic patient with a significant obsession, who was treated with a high dosage of aripiprazole and fluoxetine. Generalized tonic-clonic seizure occurred two days after abruptly stopping these two medications. Gradually tapering aripiprazole is suggested in clinical practice, especially when using a high dosage.

Keywords: Aripiprazole; High Dosage; Withdrawal Seizure

1. INTRODUCTION

Aripirazole is a so-called third-generation antipsychotic with a unique pharmacological mechanism [1,2]. It has indications for the treatment of schizophrenic and bipolar patients [3,4] and is also effective in augmenting antidepressants in neurotic patients including major depressive disorder and obsessive compulsive disorder [5-7]. Its safety and efficacy are already well-established [3,8], and few withdrawal symptoms have been reported in clinical trials. Herein, we present the case of a patient with schizophrenia, paranoid type, with significant obsession and delusion. High-dosage aripiprazole 30 mg and fluoxetine 60 mg were prescribed concurrently for three weeks for symptom relief. Generalized tonic-clonic seizure occurred two days after abruptly stopping the two medications.

2. CASE REPORT

This 40-year-old male patient had been diagnosed with paranoid schizophrenia for about 10 years. He took haloperidol 4 mg and zotepine 50 mg per day, but the response was incomplete remission. The patient still had residual psychotic symptoms including delusion of persecutory and reference under these regimens. In addition, the gradual exacerbation of significant obsession, sexual image intuition, was impacting his quality of life. Aripiprazole was prescribed and combined with fluoxetine to help control of his delusions and obsession. The score of clinical global impression-severity (CGI-S) was 5 at that time. We arranged for aripiprazole 10 mg to be taken in the first week, which was then titrated to aripiprazole 20 mg and we also added on fluoxetine 40 mg in the second and third weeks. Because the patient's psychotic symptoms and obsession still persisted, we escalated the dosage to aripiprazole to 30 mg and fluoxetine to 60 mg. The symptoms showed little improvement after one week on this high-dose regimen and his delusions even worsened. In addition, the patient also complained of akathisia. Therefore, we abruptly stopped the above two medications and set up olanzapine 10 mg specifically for his exacerbated delusions. However, generalized tonic-clonic seizure was noted the second day after stopping aripiprazole and fluoxetine. Head injury with subarachnoid hemorrhage occurred because the patient lost consciousness and fell down during a seizure. He was admitted to the Neurosurgery Ward for observation and a survey of the seizure etiologies, but no remarkable abnormality was detected, including the electroencephalography (EEG) results. The family denied a past history or family history of seizure attack. After discharge, the medication was maintained at olanzapine 10 mg, haloperidol 5 mg and escitalopram 30 mg, concurrently, for his obsession and psychotic symptoms. Under this regimen, his condition gradually improved. An EEG was arranged again four months after discharge, and still there was no abnormality noted.

3. DISCUSSION

This case involved a seizure that occurred after abruptly discontinuing a high dosage of aripiprazole and fluoxe-

tine. This is the first reported case of a withdrawal seizure related to the abrupt discontinuation of both aripiprazole and fluoxetine in combination. There are some possible explanations for the emergence of a seizure attack in this patient, including aripiprazole withdrawal, fluoxetine withdrawal, or induction by olanzapine. Aripiprazole is supposed to be at low-risk for seizure attack and the reported risk is 0.1% [9]. Only two cases of seizure during treatment with aripiprazole have been reported in the related literature and the daily dosage was 10mg and 15mg respectively [10,11]. Aripiprazole has the unique effect of dopamine stabilization, and also has a partial 5-HT1 agonist effect and antagonist activity at 5-HT2A receptors [1]. The mechanism of partial agonist effect in 5-HT1 provides efficacy, not only in treating psychotic symptoms, but also in augmenting antidepressants in the treatment of depression and obsession-compulsion [5-7]. The combination of aripiprazole and fluoxetine seemed appropriate for this case. However, fluoxetine is a cytochrome P450 (CYP) 2D6 inhibitor and aripiprazole is metabolized mainly by CYP2D6 [12]. This patient had taken the maximum recommended daily dosage of aripiprazole; however, the serum concentration may have been higher than we expected because of the inhibition of CYP2D6 by fluoxetine. Withdrawal seizure may occur when abruptly stopping such a high-level concentration of aripiprazole.

Fluoxetine has been marketed much longer than aripiprazole. The possibility of fluoxetine-induced seizure attack was around 0.1% in randomized controlled trials, and is classified as low-risk among antidepressants [13]. It has been a report of a seizure protective effect in an animal model [14]. Fluoxetine has a long half-life for 24 to 48 hours [12]. Withdrawal symptoms are fewer, compared to other antidepressants [15], and no fluoxetine withdrawal seizure has been reported so far. Thus, the seizure attack in this case more likely resulted from aripiprazole withdrawal than fluoxetine withdrawal, especially with the high concentration of aripiprazole. In most drug trials with aripiprazole, the dosage usually fell between 15 and 30 mg, and the patients seemed to tolerate this dosage well [16]. No severe withdrawal symptoms have been reported. Some adult patients have taken high-dosage aripiprazole, 45 to 75 mg per day, and all of them seemed to tolerate it well [17-19]. However, an adolescent who took 60 mg aripiprazole and 60 mg fluoxetine concurrently per day for at least three weeks revealed a blunted affect, sluggishness, and cognitive slowing [20]. These reports described the patients' condition under a high dosage of aripiprazole, so we had no idea if any withdrawal symptoms would occur when stopping such a high dosage abruptly.

This patient's seizure attack occurred on the second day after switching to olanzapine. Olanzapine probably lowered the seizure threshold [21]; the pre-marketing seizure incidence for olanzapine was about 0.9% [22]. However, this patient continued olanzapine for three months after the seizure, and no other attacks occurred. An olanzapine-induced seizure attack was therefore less likely in this case.

4. CONCLUSIONS

Aripiprazole is very frequently combined with antidepressants in clinical practice such as augmentation for refractory major depressive disorder or obsessive compulsive disorder. The potential 2D6 suppression by the antidepressants might increase the serum level of aripiprazole. Withdrawal seizure might occur when abruptly discontinuing treatment, if the patient has taken high doses of aripiprazole with an antidepressant. Thus, gradual tapering is quite important to avoid possible withdrawal symptoms including seizure attack.

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