Variations of Aripiprazole-Induced Dyskinesia Existing with Concurrent Use of Amantadine and an Anticholinergic Agent in an Elderly Patient

I-Wen Sun, Ying Lin, Shen-Ing Liu, Chau-Shoun Lee

1 Department of Psychiatry, Mackay Memorial Hospital, 2 Mackay Medicine, Nursing and Management College, 3 Department of Medical Research, Mackay Memorial Hospital, Taipei, Taiwan

Summary

Elderly patients are vulnerable to the adverse neurological effects of antipsychotics, particularly Parkinsonian symptoms and tardive dyskinesia. This vulnerability in the elderly becomes complex and unpredictable when aripiprazole is prescribed to replace other second-generation or first-generation antipsychotics. This report describes a 69-year-old female schizophrenic patient, who received aripiprazole after using a few antipsychotics, including the first- and second-generation ones. The tardive dyskinesia developed 6 weeks after switching to aripiprazole but subsided 4 weeks later when stopping the concurrent amantadine and decreasing the dosage of trihexyphenidyl. However, Parkinsonian symptoms developed insidiously thereafter, which remitted after the dosage of trihexyphenidyl was increased again. The possible mechanisms of the alternated adverse neurological events after a switch to aripiprazole in the chronic elderly psychosis are discussed.

1. Introduction

The number of elderly psychiatric patients treated with a second-generation antipsychotic has increased significantly in recent years. Aripiprazole, a second-generation antipsychotic, is a partial agonist on the dopamine type-2 (D2) and serotonin type-1 (5-HT1A) receptors as well as a full antagonist on the serotonin type-2 (5-HT2A) receptor. At the therapeutic dosage of 10–30 mg/day, aripiprazole is generally well tolerated, and the manufacturer lists an overall incidence of extrapyramidal syndrome of 6% with aripiprazole. However, elderly patients are vulnerable to adverse neurological effects of antipsychotics, particularly Parkinsonian symptoms and tardive dyskinesia (TD). This vulnerability becomes complex and unpredictable when aripiprazole is used in place of other second- or first-generation antipsychotics. Reports of adverse neurological effects induced by aripiprazole and their clinical courses have increased our understanding of the mechanisms underlying those adverse events and how to optimize the therapeutic switch from other antipsychotics to aripiprazole.

This report describes a 69-year-old female schizophrenic patient who developed 4-week temporary TD at 6 weeks after the switch to aripiprazole. The TD disappeared after stopping concurrent amantadine use and decrement of trihexyphenidyl; however, insidious Parkinsonian symptoms developed thereafter. The possible mechanisms of the alternated adverse neurological events after a switch to aripiprazole in chronic elderly psychosis are discussed.

2. Case report

Mrs. A, aged 69, was diagnosed with a schizophrenic disorder roughly 30 years ago. No substance, such as amphetamines, or alcohol use disorder was noted. The patient presented to the psychiatric outpatient clinic at a general hospital after experiencing bucco-lingual-masticatory movement for 2 weeks. Aripiprazole was used for 2 months concurrent with amantadine and trihexyphenidyl. Treatment with aripiprazole was continued because of its efficacy for psychotic symptoms, but amantadine and trihexyphenidyl treatment was stopped under the impression of TD. Within 2 weeks, the patient’s TD subsided, but Parkinsonism-like symptoms developed gradually during the following 2 weeks. Fortunately, overall involuntary movements remitted in the following year after increasing the trihexyphenidyl dosage to 10 mg/day.

The patient's long-term psychiatric treatment history was reviewed. This patient began attending our psychiatric clinic 9...
years ago when she suffered a prominent Parkinsonism-like syndrome, bradykinesia and rigidity, secondary to the use of flupenthixol at 3 mg/day. No apparent positive symptoms, like auditory hallucinations or delusion, existed under flupenthixol treatment. The patient denied any family history of major neurological disorders or involuntary movement. The adverse neurological effect of Parkinsonism-like syndrome was very distressing with obvious social functioning impairment. The patient was therefore prescribed amantadine at 200 mg/day, and the trihexyphenidyl dosage was increased from 4 to 10 mg/day. With these medications, the patient lived a reasonable life with mild but persistent Parkinsonian-like symptoms until 3 years ago, when further dyskinetic movements of her lower lip and oral area developed. The Parkinsonian-like symptoms until 3 years ago, when further dyskinetic movements of her lower lip and oral area developed. The patient then switched to risperidone at 3 mg/day briefly, and then changed to amisulpride at 400 mg/day due to intolerability. To further decrease the Parkinsonism-like syndrome and peri-oral dyskinesia, amantadine at 200 mg and trihexyphenidyl at 10 mg/day were maintained, and the amisulpride dosage was reduced to 200 mg/day about 1 year ago. Both adverse neurological symptoms subsided gradually. At that time, the Abnormal Involuntary Movement Scale (AIMS) was used to measure her motor dysfunction and the score was 2. However, her psychotic symptoms, such as auditory hallucinations, irritability, and delusion of persecution, relapsed. Therefore, amisulpride was switched to aripiprazole at 10 mg/day, and the same trihexyphenidyl and amantadine dosages were maintained. Her psychotic symptoms improved gradually over 1 month. However, involuntary buccolingual-masticatory movements developed 2 months later with a AIMS score of 12 and a global severity of 3. Dyskinesia features were grimacing; tongue protruding, squirming, and twisting; lip smacking; blowing of cheeks; chewing; puckering and pursing of lips; and rapid eye blinking. Dyskinetic movements persisted during alert hours and severely affected normal eating and drinking. No abnormal movement of her trunk, hips, extremities, and fingers was noted. A brain computed tomography scan and laboratory test results were normal. No dementia features were found. Under the impression of TD, amantadine was discontinued and trihexyphenidyl was tapered off to 4 mg/day. Dramatically, buccolingual-masticatory movements disappeared in 2 weeks.

However, a Parkinsonism-like syndrome developed gradually 2 weeks later with noticeable rigidity, bilateral pill-rolling tremors, bradykinesia, stooped posturing, limb shaking, coarse tremors, saliva discharge, a mask-like face, and difficulty in walking. The patient's AIMS score was 6 with a global severity of 1. The trihexyphenidyl dosage was therefore increased to 10 mg/day, and remission of this neurological event was achieved in 2–3 weeks. The patient showed no TD or Parkinsonism-like syndrome in the following year.

3. Discussion

Elderly patients are vulnerable to adverse neurological events, such as Parkinsonian symptoms and TD, when using various antipsychotics. The latent period from initiating an antipsychotic to the development of Parkinsonian symptoms is typically shorter than that to TD. Some possible factors likely explain why TD occurred in advance of Parkinsonian symptoms in this elderly patient after switching to aripiprazole. First, a dopamine partial agonist such as aripiprazole takes time to stabilize dopaminergic transduction under an unstable brain microenvironment. The dopaminergic actions of aripiprazole (e.g., agonist, partial agonist, or antagonist) depend on the precise cellular milieu. In this patient, long-term use of various first- and second-generation antipsychotics may have altered dopaminergic functioning as a fluctuating status; thus, predicting the response in a given tissue is difficult, particularly under pathological condition. Second, extrapyramidal symptoms may develop at the too high dopaminergic tone (e.g., chorea) or too low condition (e.g., Parkinsonism), which is also affected by acetylcholine functioning. A partial dopamine agonist has less activity than natural dopamine and needs reduced acetylcholine function to maintain a balance between these two neurotransmitters and thereby prevent involuntary movement. The dopaminergic tone (associated with amantadine) and anticholinergic tone (associated with trihexyphenidyl) in the nigrostriatal dopamine system modify the functional manifestation of aripiprazole and promote D2 receptor activation, explaining the emergence of TD in this patient, as indicated in previous reports. Third, a decreased brain neuron reserve makes elderly people sensitive to the adverse neurological effect of a dopamine partial agonist. Finally, the motor abnormality inherent in this schizophrenic patient may increase TD vulnerability. Moreover, aripiprazole is a 5-HT2A receptor antagonist that increases dopamine release, which may contribute to the appearance of TD under dopamine receptor supersensitivity.

The widely accepted mechanism of antipsychotic-induced TD is correlated with prolonged blockade of postsynaptic dopamine receptors and its aftermath of dopaminergic upregulation at the nigrostriatal pathway. When aripiprazole functioned like a dopamine full agonist on the supersensitive dopaminergic receptors and resulting in the development of TD, concurrent usage of amantadine (further increasing dopaminergic functioning) and trihexyphenidyl (affecting the balance between dopamine and acetylcholine) may exacerbate this adverse event. However, dopaminergic supersensitivity decreased gradually under the continuous use of aripiprazole. Amantadine was discontinued and the trihexyphenidyl dosage was tapered off soon after TD developed. The TD then subsided, and dopaminergic receptor functioning recovered. Under this status, aripiprazole would alternatively further downregulate dopaminergic neurotransmission in an elderly female with age-related neuronal loss and reduced brain reserve. Parkinsonian symptoms appeared instead of TD at this stage. As the functioning of acetylcholine was decreased by increasing the trihexyphenidyl dosage, the balance between cholinergic and dopaminergic transmission was reestablished and Parkinsonian symptoms disappeared. Although this patient had several risk factors for developing TD and Parkinsonian symptoms (i.e., female sex, old age, and prior extrapyramidal adverse effects), remission with no abnormal movement was successfully maintained for the following 12 months, indicating that the dopamine partial agonist is relatively safe for long-term use. The clear temporal association of initiation of aripiprazole, discontinuation of amantadine, and reduction of the trihexyphenidyl dosage with subsequent remission of TD suggests the possible etiological effect of aripiprazole on TD onset in combination with amantadine and/or trihexyphenidyl.

4. Conclusions

In line with previous reports, this report heightens the awareness of clinicians of the potential risk of various movement disorders during aripiprazole therapy for elderly patients. Interventions for extrapyramidal symptoms must be tailored to the patient's state. However, the applicability of this report is limited as it is a single-case report.

References