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CASE REPORT



The impact of aripiprazole on INR in a psychotic patient during warfarin therapy

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ABSTRACT

Aripiprazole is an atypical antipsychotic drug commonly used in the treatment of negative and positive psychotic symptoms in patients with schizophrenia, other psychotic disorders and bipolar disorder. Sagittal sinus thrombosis and transverse sinus thrombosis are the manifestations of venous thromboembolism. Warfarin is used in the treatment of venous thromboembolism. Antipsychotic treatment should be used with caution when psychotic symptoms develop in patients receiving thrombosis therapy. It is known that the risk of thrombosis increases in patients receiving antipsychotic treatment. A 32-year-old female was admitted to our outpatient unit with complaints of psychotic symptoms. The patient was using warfarin therapy for thrombosis prophylaxis. Before aripiprazole was started, INR (international normalized ratio) value was 2.18. After a week, INR value was 8. Aripiprazole treatment was stopped and INR value returned to 2.24 after a week. This report describes a 32-year-old female patient with a diagnosis of unspecified schizophrenia spectrum and other psychotic disorder according to DSM-5 who developed an increase in INR levels during aripiprazole therapy. This side effect is important because it may sometimes be life threatening and our case is the first case showing the effect of aripiprazole on INR.

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KEYWORDS

Aripiprazole; INR; warfarin

Introduction

Aripiprazole as a dopamine serotonin system stabilizer is effective in the treatment of both positive and negative symptoms in schizophrenia [1]. Unlike other antipsychotic drugs, aripiprazole is less associated with extrapyramidal symptoms, weight gain, metabolic problems, sedation and hyperprolactinemia [1–3]. Aripiprazole for its different receptor effect profile is used in the treatment of many diseases in the psychiatry clinic practice [4]. Warfarin is an oral anticoagulant, which acts by inhibiting the extrinsic pathway for the prevention of thromboembolic disorders [5]. Atypical antipsychotics are generally known to increase the risk of thromboembolism [6]. In this case report, an enhanced tendency to bleeding as a life-threatening side effect of aripiprazole in a patient under treatment with warfarin was discussed.

Case report

A 32-year-old woman was hospitalized to the neurosurgery inpatient unit with diagnosis of sagittal sinus thrombosis, transverse sinus thrombosis and haemorrhagic parenchymal infarction, cerebral oedema and midline shift and decompressive craniotomy during postpartum period for 3 weeks, and warfarin treatment was initiated to the patient 2 years ago. There were no psychiatric complaints during hospitalization

and after discharged from the hospital. She admitted to our psychiatry outpatient clinic with delusions, anger, irritability and shouting 20 months after discharged from the hospital. Because of these symptoms, treatment with quetiapine XR 300 mg per day was initiated 4 months ago. Due to the persisting of the patient's complaints of delusions, anger, irritability, shouting and weight gaining side effect, quetiapine was stopped and aripiprazole 5 mg per day treatment was started to the patient. Target international normalized ratio (INR) value was 2–3 for this patient. Before initiation with aripiprazole, her INR was 2.18. One week after the initiation of aripiprazole 5 mg per day, the INR was 8. The patient was consulted to internal medicine and vitamin K was started due to the high risk of bleeding. There was no other medication and any other medical condition that can cause an increase in the level of INR. Aripiprazole was stopped and 1 week after the discontinuation of aripiprazole, the INR was 2.24. After INR levels returned to normal range, the patient started again aripiprazole except under medical supervision. Five days after aripiprazole was started again, the INR was 6.73. Aripiprazole was stopped again and 1 week after discontinuation of aripiprazole, the INR was 2.24. Naranjo Adverse Drug Reaction Probability Scale was evaluated as 8 points, a probable adverse effect associated with aripiprazole.

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Discussion

Here, we report a case of psychotic patient with elevated INR and increased bleeding tendency after switched the treatment from quetiapine to aripiprazole. The patient did not have any other medical condition or was not using any other drug that can cause an increase in the level of INR. Although increased bleeding tendency in a patient treated with quetiapine was reported, our patient is the first case regarding enhanced bleeding tendency associated with aripiprazole in a patient treated with warfarin [7]. Increase in the level of INR after treatment with aripiprazole suggests that aripiprazole increased the anticoagulant effect of warfarin. Several drugs such as acetaminophen, cotrimoxazole, metronidazole, voriconazole, erythromycin, amiodarone, propranolol, diltiazem and fenofibrate lead to an increase in INR levels in patients under warfarin therapy [8]. Our patient didn't use any drug except warfarin and aripiprazole. Medical conditions such as alcohol use, cancer, collagen vascular diseases, congestive heart failure, liver diseases (infectious hepatitis, jaundice), hyperthyroidism and warfarin overdose may raise INR levels, but none of this was observed in our case [9].

The mechanism of increased INR levels with aripiprazole in a patient with warfarin therapy may be cytochrome enzyme system. Both warfarin and aripiprazole metabolized via CYP 3A4, therefore competitive inhibition of CYP 3A4 by aripiprazole could cause increase in plasma warfarin levels and elevation of INR [5,10]. The second explanation may be protein binding. Aripiprazole, which is approximately 99% protein bound, may have displaced warfarin from plasma proteins, resulting in higher free concentration of warfarin. Therefore, increase in free plasma concentration of warfarin which is highly bound (99%) to plasma proteins may have led to an increase in INR levels and tendency to bleeding [5,10].

Therefore, it is evident from this case that aripiprazole which is highly protein bound should be used with caution in patients under warfarin therapy. Clinicians

should be careful about life-threatening drug interactions between aripiprazole and warfarin. If co-administration of these drugs becomes necessary, closely monitoring of INR levels is recommended.

Disclosure statement

No potential conflict of interest was reported by the author.

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