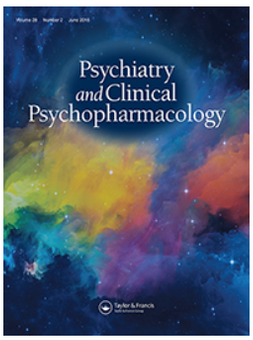

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Serhat Tunç & Hamit Serdar Başbuğ

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CASE REPORT

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An unusual complication of a long-acting injectable antipsychotic: deep venous thrombosis caused by olanzapine pamoate

Serhat Tunç [a] and Hamit Serdar Başbuğ [b]

[a]Department of Psychiatry, Faculty of Medicine, Kafkas University, Kars, Turkey; [b]Department of Cardiovascular Surgery, Faculty of Medicine, Kafkas University, Kars, Turkey

ABSTRACT

Antipsychotic drugs are widely used in psychiatry and are associated with an increased risk of adverse effects such as venous thromboembolism. Olanzapine pamoate is a long-acting injectable form of the second-generation antipsychotic agent. It is used especially in schizophrenia patients who are nonadherent to their prescription due to various reasons. Since the introduction of this newer depot form of olanzapine, it became more commonly prescribed and nearly replaced the conventional oral agent. Deep venous thrombosis (DVT) is a severe, life-threatening condition which is somehow mostly underestimated or ignored by the psychiatrists. Although the risk of DVT due to antipsychotic drug therapy has been mentioned in various studies, the relationship with olanzapine pamoate was not referred to in the available literature. Here, a DVT after the use of olanzapine pamoate was introduced.

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Long-acting; antipsychotics; deep venous thrombosis; olanzapine pamoate

Introduction

Olanzapine is a popular and well-established agent as an effective antipsychotic medication. This second-generation antipsychotic is a widely used oral medication in schizophrenia [1]. The most common adverse effects of olanzapine are weight gain and somnolence [2]. The frequent disbelief of having an illness among the patients with schizophrenia together with the unwanted side effects of antipsychotic agents results in a lack of compliance with the prescription. Therefore, the long-acting injectable (LAI) antipsychotic agents such as olanzapine pamoate were developed as a remedy for treating these schizophrenia patients whose relapses are mainly due to nonadherence to their antipsychotic medication [3]. Depot form of the antipsychotics thus reveals certain advantages relative to oral medications. If the patients discontinue their depot medication, this will immediately be recognized and interfered by the clinician [1].

Deep venous thrombosis (DVT) is a severe and potentially fatal disorder that usually complicates the course of treatment of all patients [4]. Although the thrombosis may occur in any section of the venous system, it arises mostly in the deep veins of the leg [5]. DVT affects a significant number of people, many of whom further develop post-thrombotic syndrome or pulmonary embolism (PE) as a sequela [6]. This widespread medical problem may occur either by itself or as a complication of other diseases, procedures, or medications [7]. In several studies, psychiatric disorders and the medications used for them are also accused of the development of DVT. The increased risk of DVT in patients who are treated with antipsychotic drugs has been reported in several cases [8]. Clozapine is noticeably the most mentioned drug with thromboembolic complications, but olanzapine is also subject to many reports [9].

To the best of our knowledge, LAI antipsychotic drug-related DVT is firstly described in the literature.

Case presentation

A 24-year-old male schizophrenia patient was admitted with the complaints of swollen and painful left leg. According to his past medical history, an antipsychotic olanzapine pamoate was injected two weeks ago for the first time. This LAI antipsychotic agent was administered upon his noncompliance with the previous oral treatment. Schizophrenia was diagnosed, and oral olanzapine was started one year ago. However, his denial about his diagnosis resulted in discontinuance of prescribed medication. On mental status examination, an uncooperative behaviour and increased psychomotor activity, with rare hallucinations were noted. Therefore, an alteration of the antipsychotic agent from oral form to a depot form was inevitably done. However, a week after the first dose of olanzapine pamoate injection, his left leg increased in diameter, became swollen, and painful. His past medical history revealed no immobilization, restraint, or hypercoagulable medications. According to the Naranjo Adverse

CONTACT Serhat Tunç drserhattunc@gmail.com Department of Psychiatry, Faculty of Medicine, Kafkas University, Pasacayiri, Kars 36100, Turkey

Drug Reaction Probability Scale (which showed a score of 6), this adverse effect was probably induced by olanzapine pamoate [10]. He was a non-smoker with a body mass index of 21.

The consultation with the cardiovascular surgery department revealed a femoropopliteal DVT in his left leg. The duplex ultrasound demonstrated the thrombus material inside the left common femoral vein and popliteal vein. The biochemical test showed increased D-dimer levels. No protein C or S deficiencies or any factor abnormalities were detected. Blood cell counts and the blood geometry were normal. The haemoglobin levels showed a slight increase of 14.2 mg/dl. The patient was hospitalized as a precaution to prevent an unwanted complication such as PE. A low molecular weight of heparin enoxaparin (12,000 IU/d), acetylsalicylic acid (ASA, 100 mg/d), ampicillin–sulbactam (2000 mg/d), and diosmin–hesperidin (1000 mg/d) were started. Antiembolic elastic stockings were applied. On the seventh day after the initiation of treatment, DVT was regressed and dissolved with leaving no residual thrombi. The patient was discharged on the 10th day after prescribing ASA (100 mg/d) and warfarin (5 mg/d) as maintenance. The patient was recommended to have international normalized ratio (INR) measurement every two weeks and to keep INR between 2.0 and 2.5.

During the scheduled outpatient visits in the next six months, no signs of DVT were observed despite the constant injections of olanzapine pamoate in every four-week intervals. Warfarin was then stopped in the sixth month, and the ASA (100 mg/d) was continued together with the present LAI antipsychotic agent.

Discussion

It is well known that the antipsychotic agents may cause numerous metabolic side effects such as dyslipidemia, obesity, hyperleptinemia and diabetes mellitus [11]. Antipsychotic drugs have also been proven to be associated with DVT [12]. Several suspected cases of DVT related to first-generation antipsychotics were reported in various papers published between 1953 and 1984 [13]. However, in later studies, the DVT-related hospitalization incidence was found even higher for users of second-generation antipsychotics (olanzapine, clozapine, risperidone, quetiapine) than the first-generation [14]. On the other hand, clozapine is the most reported second-generation antipsychotic with epidemiological evidence of DVT [12]. In contrary to clozapine, there are only a few published case reports about the olanzapine–DVT relationship in which the oral form was utilized [15,16].

Olanzapine pamoate is an LAI form of olanzapine combined with the salt of the pamoic acid [17]. After injection into the gluteal muscle, the two components slowly dissociate into olanzapine and pamoic acid. The dissolution of the pamoic acid salt is slow, enabling a gradual release of olanzapine into the circulation over two to four weeks [18]. Other depot forms of LAI antipsychotics have a different mechanism to achieve the slow absorption. Most of the first-generation antipsychotics carry a terminal alcohol (-OH) which enables them to combine with carboxylic acids by esterification. However, the second-generation antipsychotics lack an alcohol (-OH) terminal suitable for esterification and present a different release mechanism. The dissemination thus occurs mainly by encapsulation of the drug into a degradable polymer (risperidone) and injection of a suspension of drug compound (olanzapine) [19]. The peak concentration of olanzapine pamoate is achieved in four days with a half-life of 26 days. Olanzapine plasma concentrations are sustained throughout two to four weeks of injection intervals [17]. This is an important pharmacokinetic feature as the timing of onset after injection is the primary concern for the clinician. Therefore, some strategies were recommended for the transition from oral to LAI form of olanzapine [18]. The starting LAI olanzapine dose should be 210 mg every two weeks or 405 mg every four weeks in patients who were stabilized with 10 mg of an oral dose. The dose may then be reduced after two months to a lower maintenance dose of 150 mg every two weeks or 300 mg every four weeks. For the patients who are stabilized with 15 and 20 mg of oral form, the initial LAI doses should be adjusted as 300 mg every two weeks. After two months, the maintenance doses then should be dropped to 210 mg every two weeks or 405 mg every four weeks in patients using 15 mg daily dose. However, the patients who are stabilized with 20 mg oral dose of olanzapine should remain at the level of 300 mg every two weeks as long as the clinical indication persists [20].

The incidence of venous thromboembolism (VTE) including DVT and PE is around 1 per 1000 in the United States. Mortality is seen approximately in 6% of DVT and 10% of PE patients in one month. The acquired risk factors include the age, immobilization, smoking, obesity, pregnancy, heart failure, diabetes mellitus, surgery, autoimmune disorder, physical restraint, antipsychotics, and malignancy [21]. Schizophrenia is a chronic disabling severe brain disorder. The lifetime prevalence of schizophrenia is around 1% worldwide. Schizophrenia patients suffer from physical problems more than the general population [22]. It is also known that there are several risk factors in schizophrenia patients related to DVT and PE. Patients with schizophrenia may present with a long-term, negative cognitive or affective symptoms such as alogia, flat affect, apathy, asociality, anticipatory anhedonia, or avolition [23]. However, avolition was found to be mostly related to motor activity among the schizophrenia patients [24]. Therefore,

immobilization may be the sole cause of DVT and PE in these patients with a decreased motor activity. On the other hand, high smoking rates also increase the incidence of DVT and PE among the schizophrenia patients [25]. None of these risk factors and the possible causative scenarios existed in this patient. He was a non-smoker, with a normal motor function and mobility. He also never experienced a thrombotic event before. Therefore, the DVT was thought to be associated directly with the initial dose of the LAI antipsychotic agent olanzapine pamoate. No similar complications of DVT were mentioned before with this LAI antipsychotic agent in the available literature.

In conclusion, antipsychotic drugs are associated with increased risk of DVT. This complication may cause morbidity and mortality among people with schizophrenia who are treated for their behavioural disorders with these medications [26]. These antipsychotic drugs, specifically olanzapine pamoate, should be used more cautiously among the patients at a high risk of VTE. The patients should be informed about the risks and benefits of this medication. However, before constituting the thromboembolic risk stratification, the individual factors such as age, gender, smoking status, and the comorbidities should also be taken into consideration. Moreover, the psychiatrists should always be aware of the thromboembolic complications and side effects of these agents, and they should monitor these patients more closely. The prescription of a prophylactic antithrombotic medication such as ASA should also be considered according to the risk status of the patient upon consultation with the cardiovascular surgery department.

Disclosure statement

No potential conflict of interest was reported by the authors.

ORCID

Serhat Tunç http://orcid.org/0000-0002-2057-4074
Hamit Serdar Başbuğ http://orcid.org/0000-0002-1363-6783

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