Paliperidone: As a Possible Cause of Pericardial Effusion

Paliperidon: Muhtemel Bir Perikardiyal Efüzyon Nedeni

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ABSTRACT

Paliperidone which is the active metabolite of risperidone is one of the novel antipsychotics. Controlled clinical studies proved its effectiveness on decreasing the positive and negative symptoms of schizophrenia. Some studies and case reports, reported its cardiovascular and cardiometabolic side effects. Cardiac tamponade, that may be mortal, wasn't reported as a side effect with paliperidone usage before. We present a 40 years old female with catatonic schizophrenia for eighteen years, whom was on 6 mg/day paliperidone for 3 years and presented with pericardial tamponade. We suggest that paliperidone may have cardiovascular and cardiometabolic side effects also in therapeutic doses. (*Archives of Neuropsychiatry 2014; 51: 169-171*)

Key words: Paliperidone, pericardial effusion, cardiotoxic side effects of antipsychoticse

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ÖZET

Risperidonun aktif metaboliti olan paliperidon piyasadaki yeni atipik antipsikotiklerden birisidir. Kontrollü klinik çalışmalarda paliperidonun şizofreni tedavisinde pozitif ve negatif belirtilerin azaltılmasında etkili olduğu görülmüştür. Bazı çalışmalar ve vaka bildirimlerinde kardiyovasküler ve kardiyometabolik etkileri bildirilmiştir. Bugüne kadar paliperidonun ölümcül bir yan etki olan kardiyak tamponada yol açtığı bildirilmemiştir. Bu olguda on sekiz yıldır katatonik şizofreni tanısıyla takip edilen ve son 3 yıldır paliperidon 6 mg/gün kullanan 40 yaşındaki bir kadın hastada perikardiyal tamponad gelişimi sunulmaktadır. Paliperidonun terapötik dozlarda bile kardiyovasküler ve kardiyometabolik yan etkilerinin olabileceği tartışılmaktadır. (*Archives of Neuropsychiatry 2014; 51: 169-171*)

Anahtar kelimeler: Paliperidon, perikardiyal efüzyon, antipsikotiklerin kardiyotoksik yan etkileri

Çıkar Çatışması: Yazarlar bu makale ile ilgili olarak herhangi bir çıkar çatışması bildirmemişlerdir.

Introduction

Currently, atypical antipsychotics are being used with a gradually increasing frequency in many psychiatric diseases including mainly schizophrenia and bipolar disorder. The accumulated information in recent years has shown that the cardiac side effects of this group of drugs have vital importance. The cardiac side effects related with antipsychotics include many clinical pictures including weight gain, lipid and glucose metabolism disorders, metabolic syndrome and cardiovascular risk, orthostatic hypotension, tachycardia, arrhythmia and sudden death, cardiomyopathy, myocarditis, pericarditis and pericardial tamponade (1).

Antipsychotic drugs may have both antiarrhythmic and arrhythmogenic effects on the heart. Because they antagonize the sympathetic activity in the hypothalamus and show local anesthetic action, they stabilize the myocardial cell membrane and may show antiarrhythmic effect in this way. It depends on

the drug and dose used and the patient's cardiac status if antipsychotic drugs have protective or toxic action on the heart (2).

Myocarditis and cardiomyopathy are rare side effects of antipsychotics, but may be fatal. Although cardiomyopathy and myocarditis are most commonly observed with clozapine, these side effects may also be observed with the other antipsychotics. Pericarditis and pericardial tamponade have been reported with use of clozapine, though very rarely, in addition to myocarditis and cardiomyopathy. It has been reported that clozapine-related pericarditis may have a clinical picture ranging from pleuretic chest pain to cardiac tamponade and the symptoms have been reported to improve with discontinuation of the drug in almost all cases reported (3).

In this article, a case of pericardial effusion which probably developed as a result of use of paliperidone at a dose of 6 mg/day is presented and possible cardiac mechanisms are discussed.

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Case

A 40-year old female patient who had been followed up with a diagnosis of catatonic schizophrenia for eighteen years and had been using paliperidone at a dose of 6 mg/day for 3 years presented to the emergency department of our university with complaints of dyspnea and chest pain. On physical examination, her general status was moderate, consciousness was open, the arterial blood pressure was found to be 80/60 mmHg and the pulse rate was found to be 125/min and regular. The heart sounds were weak. Examinations of the other systems were found to be normal. Electrocardiogram revealed sinus rhythm and QRS voltage loss. On echocardiogram, findings of cardiac tamponade were observed and pericardiocentesis was performed for treatment. There was no history of any cardiac or systemic additional disease. There was no history of use of additional medication (psychotropic and other drugs) in combination with paliperidone. Consultations with the divisions including infectious diseases, nephrology, rheumatology and internal medicine were made in terms of causes which could lead to pericardial effusion including pericarditis, malignancy, acute myocardial infarction, end-stage renal disease, congestive heart failure, collagen vascular disease and viral and bacterial infections (4). Routine biochemistry tests, renal and hepatic function tests, complete blood count, erythrocyte sedimentation rate, coagulation tests, examination of pericardial fluid and culture tests were performed. The results of the routine biochemistry tests, renal and hepatic function tests, complete blood count, erythrocyte sedimentation rate and coagulation tests were found to be normal. The pericardial fluid had the characteristics of an exudate and no growth occurred in the culture of the pericardial fluid. Atypical cell was not observed on cytological examination of the pericardial fluid. With these results, the diagnoses which could lead to pericardial effusion mentioned above were excluded. No cause which could explain the etio-pathogenesis of pericardial effusion could be found and it was thought that this was probably related with use of paliperidone. After discharge, paliperidone was discontinued and aripiprazole was initiated. The dose of aripiprazole was gradually increased up to 20 mg/day. Cardiac tamponade symptoms were not observed at monthly follow-up visits for six months after initiation of aripiprazole and the findings of transthoracic echocardiography were completely improved. The patient had a BPRS score of 21 and her psychiatric and neurological examinations were found to be normal. The patient is still being followed up with regular follow-up visits.

Discussion

Paliperidone which is the active metabolite of risperidone is one of the new atypical antipsychotics on the market. In controlled clinical studies, it has been observed that paliperidone is effective in decreasing positive and negative symptoms in treat-

ment of schizophrenia. The drug shows therapeutic effect as a central dopamine type-2 (D2) and a serotonin type-2 (5HT2A) receptor antagonist. It has some side effects, because it shows antagonistic effect on adrenergic and histaminergic receptors. In more than 2% of the patients, clinical side effects including tachycardia, abdominal pain, nausea, dry mouth, extrapyramidal symptoms, dizziness, anxiety and somnolence may be observed (5).

In a study conducted by Suzuki et al., paliperidone which is the metabolite of risperidone was reported to be the cause of QT prolongation related with risperidone (6). One of the mechanisms underlying QT prolongation related with antipsychotic drugs is blocking of the ion channels, slowing of depolarization and prolongation of the QRS interval. It is thought that the drugs which block sodium channels during depolarization cause to partial prolongation in QRS and are not related with sudden death in individuals who have no previous cardiac disease (5). In the study of Vigneault et al., it was reported that paliperidone caused to prolongation of QT by way of blockage of the human ether-a-go-go related gene (HERG) which codes a protein related with cardiac potassium (K⁺) channels and was potentially unsafe in terms of cardiac health (7).

The mechanism of cardiotoxic effects including myocarditis, pericarditis and cardiac effusion related with atypical antipsychotics has not been elucidated fully yet. The main hypothesis is IgE-mediated hypersensitivity reaction. The most important supporter of this hypothesis is presence of peripheral eosinophilia and increased number of eosinophils in the heart muscle on biopsy observed with cardiotoxic effect related with clozapine (8). The other important hypothesis is that clozapine which is an atypical antipsychotic increases the catecholamine level and especially noradrenaline level. The fact that increased noradrenaline is a significant factor in takotsubo cardiomyopathy which is left ventricular dysfunction has been shown as a proof for this hypothesis (9). The other less significant mechanisms include cytochrome P450 1A2 and 1A3 enzyme deficiency, blockage of calcium-dependent ion channels, increased inflammatory cytokine level and decreased selenium level (10). Although the mechanism of cardiac effusion related with atypical antipsychotics has not been elucidated fully for the present time, we think that it probably occurs as a result of interaction of many different mechanisms which are mentioned above based on the clinical data obtained. More comprehensive studies should be conducted in this area.

The reasons which suggested that cardiac tamponade in this patient could be related with paliperidone included lack of a history of use of additional drug or lack of a history of any comorbidity, lack of cardiac or metabolic problems or risk factors, improvement of the clinical picture with discontinuation of the drug and no recurrence of effusion with use of a different drug.

A case of pericardial tamponade probably related with use of paliperidone has been presented for the first time in the literature. According to the adverse drug reaction (ADR) assessment test performed in this patient, the possibility that the adverse drug reaction occurred in relation with paliperidone was

in the “probable” category by Naranjo’s ADR probability score. Although the level of the possibility of pericardial effusion related with paliperidone is not known for the present time, one should be careful in terms of cardiovascular and cardiometabolic health especially in patients for whom outpatient treatment is planned because of a high risk of life threat.

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