

Atrial Fibrillation Associated with Clozapine and Olanzapine: A Case Report



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SUMMARY

Objective: Atrial fibrillation is a serious side effect of antipsychotic drugs that is very rare but can be fatal. In this case report, a subject who developed atrial fibrillation after receiving clozapine and olanzapine has been presented.

Case: A 49-year-old female patient with a 10-year history of schizophrenia with no additional disease history was admitted to the hospital with the diagnosis of resistant schizophrenia. Clozapine was started at a dose of 12.5 mg/day and was gradually increased. When the clozapine dose was 100 mg/day (25th day of treatment), atrial fibrillation developed. Administration of the drug was stopped and the patient was monitored with daily ECG; no medicine was given in this period. One week later, clozapine was started again at a dose of 12.5 mg/day and increased to 100 mg/day. Meanwhile, a single dose of 10 mg of olanzapine velotab was given to the patient in order to prevent agitation. Atrial fibrillation developed again. Holter ECG was within normal limits. Clozapine treatment was discontinued when the treatment dose reached 250 mg/day because atrial fibrillation developed again. After a drug-free period of one week, atrial fibrillation did not occur during the following haloperidol, risperidone, and quetiapine treatments.

Discussion: Because ECG and echo were within normal limits, blood pressure was normal, and no thyroid dysfunction was present, all the medical diseases that can cause atrial fibrillation were eliminated. Atrial fibrillation occurred during clozapine treatment and redeveloped after a period of cardiac stability with olanzapine treatment. The patient was stable again when treatment was discontinued; atrial fibrillation did not occur during haloperidol, risperidone, and quetiapine treatments and was not present when the patient was using other antipsychotic drugs before hospitalization. All of these findings suggest that atrial fibrillation may be related to clozapine and olanzapine, which are drugs with similar chemical structure.

Conclusion: It is especially important to monitor cardiac side effects and ECG in patients who are using atypical antipsychotic drugs. Further studies should be conducted on the relationship of antipsychotic use and cardiac arrhythmia.

Key words: antipsychotic, atrial fibrillation, clozapine, olanzapine

Recently, prescription of atypical antipsychotic drugs has become common for many psychiatric disorders, including schizophrenia and bipolar disorder. Though it is reported that these drugs have many positive effects, such as lower risk of extrapyramidal system signs, amenorrhea, galactorrhea, and late dyskinesia, and improved functionality and quality of life, studies have also shown that atypical antipsychotics may lead to weight gain, glucose and lipid metabolism disorders, metabolic syndrome, and increase in cardiovascular risk (Owens and Risch 1995). Cardiovascular side effects of antipsychotic drugs include orthostatic hypotension, syncope, long QTc,

ventricular tachycardia, myocarditis, cardiomyopathy, pericarditis, and sudden cardiac death (Anıl Yağcıoğlu and Ertuğrul 2011). It has been shown that the relative risk of death associated with cardiovascular diseases in patients diagnosed with schizophrenia increased 1/3 rate (Jeste et al. 1996, Kurt et al. 2007).

Clozapine is an atypical antipsychotic drug of dibenzodiazepine group and is used in resistant schizophrenia, schizoaffective disorder, and bipolar disorder. It reduces the risk of suicide and aggressive behavior (Meltzer 2002, Citrome et al. 2001).

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It shows high 5HT_{2A}/D₂ receptor affinity and high α_1 , M₁, H₁ receptor affinity (Anıl Yağcıoğlu and Gürel 2010).

Clozapine has a high risk of cardiac side effects (Schneider and Lizer 2008). It may lead to sinus tachycardia, orthostatic hypotension, long QT_c, and, rarely, myocarditis and cardiomyopathy (Raedler 2010, Mackin 2009).

Olanzapine shares similar structural characteristics with clozapine and shows affinity to 5HT_{2A}, 5HT_{2C}, D₂, D₃, D₄ and M₁₋₄, H₁ receptors. It is a thienobenzodiazepine derivative atypical antipsychotic (Anıl Yağcıoğlu and Gürel 2010). Like clozapine, olanzapine carries a high risk of metabolic syndrome. It has been observed that metabolic syndrome leads to cardiovascular diseases and increases the risk of cardiovascular mortality three-fold. Furthermore, olanzapine is among the antipsychotics that increase the risk of coronary artery disease development at the highest level (Lakka et al. 2002, Raedler 2010).

The most prescribed drugs in sudden death cases are antipsychotics. Sudden cardiac deaths due to antipsychotics are related to increased arrhythmia risk of these drugs, which presents as QT prolongation on ECG, ventricular tachycardia, and torsades de pointes (Anıl Yağcıoğlu and Ertuğrul 2011, Abdelmawla and Mitchell 2006). Thioridazine and pimozide, among the typical antipsychotics, and sertindole and ziprasidone, among the atypical antipsychotics, are accepted as risky in terms of QT_c prolongation. Clozapine was also reported to be associated with QT_c prolongation in a dose-dependent manner (Anıl Yağcıoğlu and Ertuğrul 2011, Kang et al. 2000).

Atrial fibrillation is fast and irregular activity of atria with loss of normal sinus rhythm. Atrial fibrillation is a supraventricular arrhythmia characterized by non-organized, high pace, atrial electrical activity. In state of p waves in electrocardiogram, fast and irregular fibrillation waves with various shapes and sizes are seen. Prevalence of atrial fibrillation is estimated to be 4% in the general population and increases with aging (Adalet et al. 2003). Atrial fibrillation may cause severe consequences such as stroke, thromboembolism, heart failure, and mortality. It is accepted that a basic trigger is required for development of atrial fibrillation. Patients generally begin with an atrial abnormality such as inflammation or fibrosis. Atrial ectopic focus, atrial wall distension changes, and autonomic tone variations may be the trigger and may lead to impaired atrial electrical activity. Atrial fibrillation feeds itself through a process called “electrical remodeling.” Loss of atrial systolic function causes irregular ventricle pace and insufficient ventricular filling, which in turn reduces cardiac output. Loss of atrial systolic function leads to left atrial congestion and formation of intra-atrial thrombus. Eventually, the risk of stroke and thromboembolism are increased. Uncontrolled high heart rates, when prolonged, lead to progressive left ventricular dilatation in myocardium and reduction in left ventricular

systolic function. Acute alcohol ingestion, surgical interventions, electric shock, pericarditis, myocarditis, pulmonary embolism, hyperthyroidism, valvular heart disease, heart failure, coronary heart disease, and hypertension accompanying to left ventricular hypertrophy are the most important causes of atrial fibrillation. Drugs may also cause atrial fibrillation (Go et al. 2001, Stewart et al. 2002). Sympathomimetic drugs and digoxin may affect autonomic nervous system, change electrical activity of atria, and result in atrial fibrillation (Nattel 2002, Mert 2006). The mechanism of antipsychotic-related atrial fibrillation remains to be elucidated. In literature, antipsychotics has been reported to elevate sympathetic tone via muscarinic receptors and reduce parasympathetic tone, which in turn leads to sudden cardiac death (Waters et al. 2008, Agelink et al. 2001). Within the literature, there are three case reports related to atrial fibrillation involving antipsychotics and cardiac side effects: two related to clozapine, two related to olanzapine, and one related to paliperidone (Simpson et al. 1978, Low et al. 1998, Waters et al. 2008, Yaylacı et al. 2011, Schneider and Lizer 2008). Here, we report a case of atrial fibrillation associated with clozapine and olanzapine use.

CASE

A 49-year old women admitted to emergency service with symptoms of irritability, aggressive behaviour, suspiciousness, insomnia, and refusing medications. She was a college graduate, unemployed, divorced, with a child. The patient was hospitalized to psychiatry service with a diagnosis of schizophrenia undissociated type according to DSM-IV (American Psychiatry Association 1994). The initial complaints of patient had started after divorce ten years ago, and included irritability and bizarre speech. Taking history revealed that she used risperidone, risperidone depot, quetiapine, and valproic acid treatments regularly, but her complaints continued. The patient received amisulpride 600 mg/day, oxcarbazepine 900 mg/day, lorazepam 1.25 mg/day, and bornaprine 12 mg/day treatments in the last year. Psychiatric examination revealed that she was conscious, cooperative, and oriented. Emotional state was limited. She was irritated. She had verbal visual hallucinations, offensive behaviour, expectancy of getting harmed, erotomanic delusions, megalomania, and delusions of control. Her associations were spontaneous and sometimes loose. Her spontaneous and voluntary attention was natural. Abstract thinking ability was impaired. Irritability and hallucinations were observable. She was sleepless and lost her appetite. There was no additional medical condition or history of cardiac disorder. No alcohol and substance use were noted. She had been smoking one pack per day for 18 years. Family history revealed no psychiatric disorders or heart attack. Thyroid function tests, electrolytes, and biochemistry were within normal limits. ECG showed normal sinus rhythm.

As she had hypertension at admittance, cardiology department started perindopril arginine 5 mg/day. Her psychotropic drugs were not stopped after hospitalization. The patient's dose of amisulpride was gradually increased to 1000 mg/day. Oxcarbazepine and lorazepam were gradually reduced and stopped. Blood pressure follow up was natural. As the psychotic symptoms maintained, she was accepted as having resistant schizophrenia and clozapine 12.5 mg/day was started. Amisulpride was reduced to 800 mg/day, and bornaprine was stopped. Diazepam 10 mg/day was added to her treatment. Three days later, amisulpride was reduced to 400 mg/day, and clozapine was increased to 25 mg/day. Diazepam was stopped by day four, as it induced too much sedation. Amisulpride was entirely stopped three days later. Under hemogram, heart rate, blood pressure, and temperature monitorization, clozapine was gradually increased to 100 mg/day.

The patient did not feel well on the 25th day of clozapine treatment (clozapine dose was 100 mg/day). Her blood pressure was 90/60 mmHg. Her pulse was weak and irregular. ECG recording showed atrial fibrillation with a high ventricular response. The cardiologist recommended metoprolol, enoxaparin sodium, acetylsalicylic acid, and warfarin. Echocardiography showed normal left ventricle dimensions and the condition was accepted as new onset atrial fibrillation due to antipsychotic use. Treatment was stopped for one week. When daily ECG recordings showed normal sinus rhythm, clozapine 12.5 mg/day treatment was started again with the approval of cardiology. Dose was slowly increased to 100 mg/day. On the day 19, single dose 10 mg olanzapine velotab was given to patient for agitation. Atrial fibrillation started again after that dose. Holter ECG was mounted. No pathology was noted. Daily ECG recordings were normal. Clozapine treatment was continued. When the clozapine dose was 250 mg/day (day 45), atrial fibrillation started again. Clozapine treatment was stopped. CG recordings were normal during one week without antipsychotic treatment. Cardiologists recommended only acetylsalicylic acid 100 mg/day. After one week drug-free period, haloperidol 15mg/day, haloperidol 15mg/day, and quetiapine 900 mg/day combination were given. At the end of the fourth week, haloperidol was stopped as the symptoms were persisting. Risperidone treatment was started and dose was increased to 8 mg/day. Three weeks later, the patient was discharged as her hallucinations and delusions were reduced, and her sleep and appetite were normal. Atrial fibrillation was not observed during the latter treatment and three months follow up.

DISCUSSION

Cardiological and other medical conditions that lead to atrial fibrillation were excluded as there was no previous history of arrhythmia and heart disease; hypertension was new onset;

left ventricular dimensions were normal; ECG recording before clozapine treatment was normal; heart rate and blood pressure follow ups were normal; laboratory tests including thyroid function and electrolytes were within normal limits. It has been reported in literature that hypertension may lead to systolic and diastolic dysfunction of ventricle, left ventricular hypertrophy, and atrial pump dysfunction, which in turn increase atrial volume and wall tension. This may stimulate collagen synthesis and promote fibrosis and hypertrophy. Hypertrophy and fibrosis may cause atrial arrhythmia and fibrillation (Brilla et al. 2000, Mattioli et al. 2005). However, hypertension was new in our patient and ventricular dimensions were within normal limits. Thus, it is unlikely that atrial fibrillation resulted from hypertension. Arrhythmia occurred when the patient was on clozapine medication. Single dose olanzapine led to atrial fibrillation in the patient with a stable cardiac condition. Atrial fibrillation disappeared after stopping medications. No atrial fibrillation was observed with amisulpride, haloperidol, risperidon, and quetiapine medications. This supports the idea that clozapine/olanzapine induced atrial fibrillation in this patient. The drug side effect scale, developed by Naranjo et al., is a 10-item questionnaire. The relationship of a drug and corresponding side effect is certain with 9 points, probable with 5-8 points, and possible with 1-4 points. Based on this scale, the relationship between clozapine and atrial fibrillation was probable (5 points), whereas the relationship between olanzapine and atrial fibrillation was possible (4 points) (Naranjo et al. 1981).

In literature, there are two clozapine-related (Simpson et al. 1978, Low et al. 1998), two olanzapine-related (Waters et al. 2008, Yaylacı et al. 2011), and one paliperidon-related (Schneider and Lizer 2008) atrial fibrillation cases.

Simpson and colleagues (1978) studies the efficacy of clozapine in 12 patients with tardive dyskinesia, and reported hypotensive shock, unmeasured blood pressure, cyanosis, and atrial fibrillation in a patient who was on 15 mg/day of clozapine. After several days of drug-free interval, clozapine was restarted and increased up to 550 mg/day without any problems.

Low and colleagues (1998) reported a 69-year-old male patient with paranoid schizophrenia for 35 years. They started clozapine medication and increased the dose up to 325 mg/day in three weeks. Positive psychotic symptoms improved, but orthostatic hypotension developed. Besides clozapine, the patient was taking doxazosin for benign prostate hyperplasia. Doxazosin was also considered as a possible contributing factor for orthostatic hypotension. Clozapine dosage was reduced to 300 mg/day and doxazosin was reduced to 2 mg/day from 3 mg/day. In the fourth week, atrial fibrillation developed. Warfarin and digoxin were added to the treatment. Both clozapine and doxazosin medications were ceased, causing normal sinus rhythm to return. Warfarin treatment was

ceased, and digoxin treatment was continued. Three days later, administration of 25mg/day of clozapine was started again, and the dose was increased to 100 mg/day at the end of first week. Doxazosin treatment was added, causing atrial fibrillation to begin again. Clozapine was stopped; diltiazem 90 mg/day treatment was started. Forty-eight hours after ceasing clozapine, normal sinus rhythm was obtained. The patient was started on olanzapine treatment. Authors stated that the mechanism of this side effect induced by clozapine was not clear, and cardiac monitorization and ECG recording might be important during clozapine dosing.

In the literature, cases of atrial fibrillation associated with olanzapine are confined to case reports. Waters et al. (2008) reported a 47-year-old male patient with bipolar disorder. He was admitted to hospital for his bizarre behavior. There was no previous history of heart diseases. He was on valproic acid medication, but it was irregular. One month prior to admission, haloperidol was given and acute dystonia developed. At the emergency room, the patient's heart rate was regular (71 min^{-1}), and blood pressure was 152/94 mmHg. Laboratory tests including thyroid functions were within normal limits. Blood and urine toxicology analyses were negative. A single dose of olanzapine (10 mg) and single dose oral diphenhydramine (50 mg) were given to the patient in order to prevent extrapyramidal symptoms. Six hours later, irregular heart rate (64 min^{-1}) developed, and blood pressure ranged between 101/70 to 110/80 mmHg. Atrial fibrillation was found on ECG, which returned to normal sinus rhythm in one hour; atrial fibrillation did not repeat. Yaylacı and colleagues (2011) reported a case of a 21-year-old female who ingested 14 tablets of olanzapine to commit suicide. She was admitted to the hospital with nausea, vomiting, and dizziness. Patient's and her family's history revealed no medical or cardiac condition. She was a nonsmoker, and no alcohol or substance use was noticed. Her blood pressure and heart rate were 110/80 mmHg and 70 bpm, respectively. ECG showed normal sinus rhythm. Gastric lavage was performed. Atrial fibrillation was noted 4 hours later, which returned to normal sinus rhythm in 10 minutes. Arrhythmia was considered to be associated with olanzapine use as there was no history of other pathologies that cause arrhythmia, the event occurred 4 hours after olanzapine ingestion, and spontaneous remission occurred. Authors pointed out the need for further studies to shed light on the effects of new antipsychotics on cardiac rhythm. In addition, Ciszowski and Sein Anand (2011) suggested serum olanzapine toxic dose 100 ng/ml in 23 patients with olanzapine intoxication. They also evaluated ECG recordings and found prolonged QTc interval and fast supraventricular arrhythmias were common. They found irregular tachyarrhythmias such as atrial fibrillation rare.

Schneider and Lizer (2008) reported a 46-year-old male patient with atrial fibrillation. He was diagnosed with bipolar

disorder and started escitalopram, lamotrigine, and clonazepam. Paliperidone was added and the dose was adjusted to 3 mg/day on the first day, and then increased to 6 mg/day. Four days later, atrial fibrillation developed. Patient's history revealed diabetes mellitus, hypertension, and hyperlipidemia under control. He was a smoker. No previous arrhythmia, food allergy, dietary supplement use, or herbal remedy use was noted. His prescription was not changed except for the addition of paliperidone. According to Naranjo et al., the relationship between paliperidone and atrial fibrillation scored 4 points. Oral acetylsalicylic acid and heparin infusion were given to the patient. Following diltiazem 10 mg intravenous administration, normal sinus rhythm was achieved. No atrial fibrillation was noted during 30 days follow up.

Especially in patients who are on atypical antipsychotic treatment, cardiac side effects should be monitored. When deciding to start antipsychotic agents, cardiovascular risk factors should be evaluated. In patients who carry cardiac arrhythmia risk factors, such as ischemic heart disease, electrolyte imbalance, thyroid diseases, liver and kidney diseases, and a family history of cardiac diseases, antipsychotics with lesser effects on cardiac repolarization should be chosen. High doses should only be used when necessary. It is recommended that ECG is recorded before starting therapy. Left ventricular hypertrophy should be checked and electrolyte levels, mainly potassium, should be monitored. Antipsychotic summary of product characteristics recommend ECG recording at higher doses and cardiac monitorization in patients receiving parenteral therapy. Some references suggest annual ECG recording in patients who are on antipsychotic therapy. ECG should be repeated in case of palpitation, dizziness, syncope, QTc prolongation, or additional drug use. For sertindole, ECG is recommended before treatment, before and after each dose adjustment, and every three months (Mackin 2009, Anıl Yağcıoğlu and Ertuğrul 2011, Fayek et al. 2001). The biggest contribution to cardiovascular disease risk comes from metabolic syndrome. The American Diabetes Association recommended annual control of family and personal history in atypical antipsychotic use, together with body mass index initially and every month during the first year, then every three months. Waist circumference should be checked initially and then annually; blood pressure should be controlled initially, at third month, and then annually. Lipid profile should be controlled initially, at third month, and then at every five years (American Diabetes Association 2004). The Turkish Psychiatry Society recommended a similar follow-up plan in schizophrenia treatment guideline (Saka et al. 2005).

Blood concentrations of olanzapine and clozapine were not measured in our case. Genetic analyses of cytochrome enzymes were not performed. Cytochrome P450 isoenzymes CYP1A2 and CYP2D6 play a role in the formation of olanzapine metabolites, whereas CYP1A2 and CYP3A4 play a role

in the formation of clozapine metabolites. Genetic variations may influence enzyme activity and alter the blood level and side effects of the drug. Therefore, evaluation of enzyme activity besides measuring blood levels of the drug may disclose the relationship of drug and side effect (Herken et al. 2001). Drug interactions should also be considered. No pharmacodynamic and pharmacokinetic interaction was noted between perindopril arginine and clozapine/olanzapine.

Further studies should be performed to shed light on the mechanisms of arrhythmia and atrial fibrillation induced by atypical antipsychotics. Physicians should be careful for cardiac side effects when prescribing atypical antipsychotic drugs.

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