European Review for Medical and Pharmacological Sciences 2014; 18: 2383-2386

Myocarditis after administration of Clozapine

K. KONTOANGELOS[1,2], S. LOIZOS[3], J. KANAKAKIS[3], N. SMYRNIS[1], M. ECONOMOU[1,2], J.D. BERGIANNAKI[1,2], G.N. PAPADIMITRIOU[1]

[1]1st Department of Psychiatry, Athens University Medical School, Eginition Hospital, Athens, Greece
[2]University Mental Health Research Institute, Athens, Greece
[3]University of Athens School of Medicine, Department of Clinical Therapeutics, Alexandra Hospital, Athens, Greece

Abstract. – OBJECTIVE: Clozapine is an atypical antpsychotic medication with established efficacy in patients diagnosed of resistant schizophrenia. However, clozapine has multiple side effects. Cardiac complications such as myocarditis and cardiomyopathy have always been related with treatment with clozapine.

METHODS: A 42 year old Caucasian male, with history of schizophrenia developed a acute myocarditis after commencement of clozapine.

RESULTS: The patient recovered with intensive medical support. The symptoms occurred approximately 20 days after starting clozapine.

CONCLUSIONS: Myocarditis is an ingreasingly recognized complication associated with clozapine. Use of clozapine must be based on a balance of its risks and benefits on an individual basis which for the most part defines its use in treatment refractory schizophrenia. Appropriate monitoring of adverse events is an essential part of the clinical usage of clozapine and should be charted for at least two years.

Key Words:
Myocarditis, Clozapine, Angiography, Drug safety, Side effects.

Introduction

Clozapine has multiple side effects and among others myocarditis and cardiomyopathy have been closely related with this treatment[1]. This association was confirmed in 1999 by Killian et al[2] in 15 cases of myocarditis and 8 of cardiomyopathy among 8000 patients treated with clozapine. The majority of suspected myocarditis reports reported between 2000 and 2003 propably be increased awareness of the problem following the publication of the paper by Killian et al in 1999. The median age of patients with suspected myocarditis was 30 years amongst 110 cases in which age was a known characteristic. Myocarditis dents to appear at any time during treatment with clozapine but a particular "dangerous period" appears to exist during the first 4 weeks following initiation of clozapine therapy[3]. We present a case of patient who developed acute myocarditis related with clozapine treatment.

Case Report

The patient is 42 year old Caucasian male, of BMI 24.9 kg/m^2, with history of schizophrenia diagnosed 20 years ago and treatment-resistant schizophenia. In the past, patient had been treated initially with risperidone and haloperidol. However, two years ago, after presenting auditory and visual hallucinations and being hospitalized, he was started on olanzapine and haloperidol, and later on risperidone without efficient management of the disease, hence clozapine treatment was considered. Patient was started on clozapine 12.5 mg o.d., tritated gradually to 50 mg t.i.d. on the fifteenth day of treatment, without presenting any adverse effects.

On day 18 of treatment with clozapine, the patient being treated on 150 mg clozapine daily at that time, he complained of palpitation, tachycardia, dyspnoea and fatigue and he was transferred to A&E(accident and emergency). The clinical examination revealed unusually low for the particular patient blood pressure (95/60 mm Hg), tachycardia (110 beats/min) and the ECG (Figure 1) revealed ST-elevation on precordial leads V_1-V_3, ST-depression on inferior and lateral leads, suggesting myocardial ischemia, despite the fact that patient did not complain of chest pain. Additionally, mild troponin-T elevation was found (0.24 mcg/L, normal < 0.1 mcg/L) and patient was admitted in the CCU (coronary care unit). Emergency echocardiography indicated mild left ventricle systolic dysfunction (EF 40-45%) (ejection fraction), with anterior and lateral wall hy-

Corresponding Author: Konstantinos Kontoangelos, MD; e-mail: kontange@hol.gr

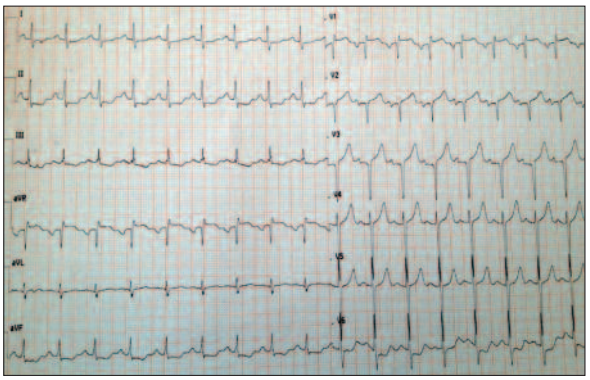

Figure 1. Patient ECG at admission.

pokinesia, grade 1 diastolic dysfunction, moderate mitral regurgitation, enlarged left atrium and global left ventricular wall hypertrophy. Further laboratory tests revealed renal dysfunction [Serum creatinine 2.36 mg/dL, (Blood urea nitrogen) BUN 51 mg/dL, Creatinine clearance 49 ml/min] and elevated WBC (White blood cell) count (15,200 cells/mcL).

Under the suspicion of ST-elevation myocardial infarction, an emergency left catheterization was performed, which indicated coronary arteries without lesions and normal (TIMI 3) flow (Figure 2). Patient returned in the CCU hemodynamically stable condition and the sheath was removed without complications. The possibility of thrombus in the coronary arteries, Prinzmetal's angina or acute myocarditis was considered. Despite the difficulty in retrieving information from the patient due to his mental condition, patient did not seem to have experienced flu-like symptoms lately, fever or chest pain of any kind. On the other hand, the onset of symptoms on day 18 of clozapine treatment raised the suspicion for clozapine-induced myocarditis and the drug was discontinued immediately. After consulting the Department of Psychiatry at Eginition Hospital, only diazepam and haloperidol was continued from his psychiatric treatment. Three hours post the coronary angiography, patient presented symptoms of cardiogenic shock, with sweating, peripheral vasoconstriction, severe hypotension and worsening of renal function. Emergency echocardiogram indicated severe left ventricular systolic dysfunction, with estimated EF 20-25% and global support and hypokinesia. Dobutamine and noradrenaline were administrated for hemodynamic emergency right heart catheterization confirmed severe cardiac systolic impairment (cardiac index 1.7 L/min, cardiac output 3.6 L/min) with increased systolic and pulmonary resistance (1743 dyn·s/cm^5 and 4.1 Woods respectively). Due to hemodynamic deterioration despite inotrope administration, intra-aortic balloon pump (IABP) was inserted, followed by gradual patient stabilization and patient maintained a mean pressure

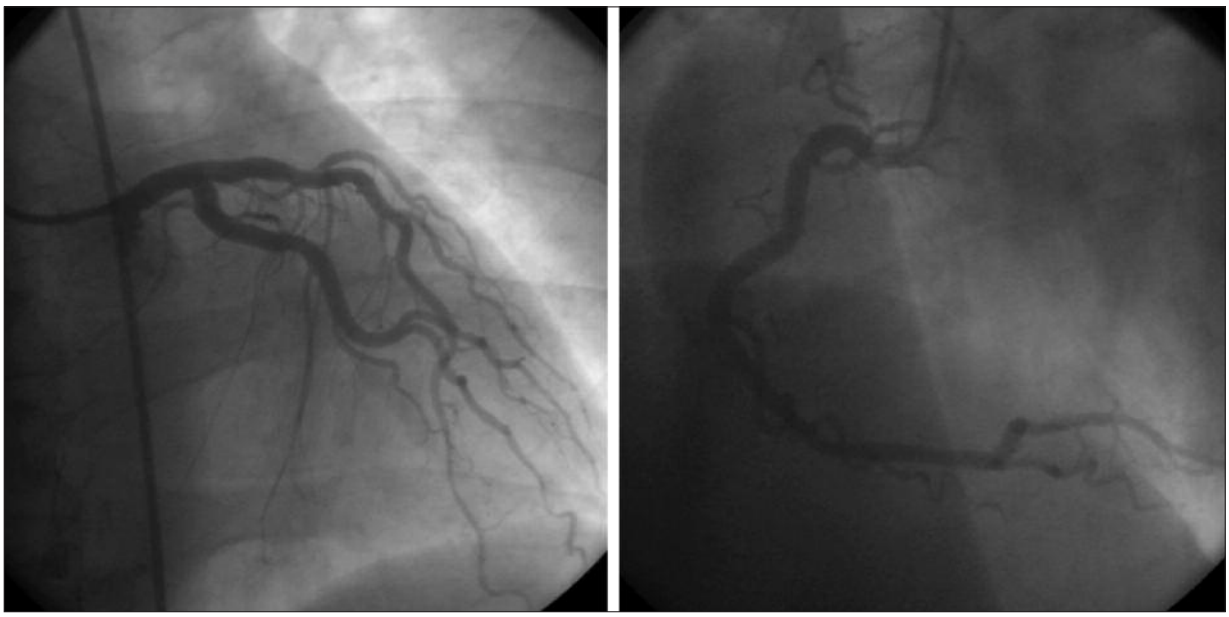

Figure 2. Angiogram of left (*left image*) and right (*right image*) coronary arteries.

80-90 mmHg. Norepinephrine administration was stopped 12 hours later, however dobutamine administration was continued. New laboratory tests revealed increase of troponin-T and CPK (creatine phosphokinase) levels (5.2 mcg/L and 208 mcg/L respectively), further increase of WBC count (16,700 cells/mcL) and very high CRP(C-reactive protein) levels (190 mg/L, normal < 10 mg/L). New right heart catheterization, with continuous inotrope administration and patient in intra-aortic balloon pump (IABP), indicated improvement of cardiac systolic function (cardiac index 2 L/min, cardiac output 4.4 L/min) and increased pressures in right ventricle and pulmonary artery (63 mm Hg). A thorough virus investigation was performed to exclude other cause of myocarditis, which indeed was negative. Blood cultures and immunology tests were also negative. Renal function deteriorated (creatinine clearance 37 mL/min), Troponin-T levels increased to 29 mcg/L and BNP(B-type natriuretic peptide) was 2213 pg/mL and patient was started on furosemide. On day 3 the administration of inotropes was discontinued and patient maintained a mean pressure 80 mm Hg, assisted by the IABP. Renal function gradually improved (Creatinine clearance 50 mL/min) and WBC count returned within normal limits (9100 cells/mcL). An echocardiography study indicated improvement of left ventricular systolic function (EF 40%) with global hypokinesia and good right ventricular systolic function. Patient ecg did not markedly changed compared with the admission ecg, ruling out the hypothesis of an acute coronary syndrome (Figure 3). However, on day 4 patient presented atrial fibrillation which resulted in mild hemodynamic destabilization (mean preassure 70 mm Hg). Numerous attempts for drug (amiodarone) and electric cardioversion were unsuccessful. Patient was started on digoxin for rate control, maintaining a basic rhythm of atrial fibrillation with mean HR 110 beats/min.

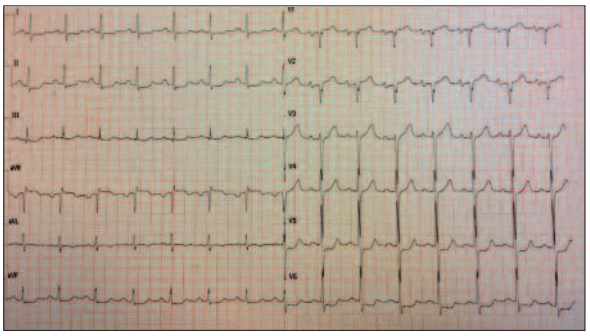

Figure 3. Patient ECG on day 4.

On day 5, laboratory tests indicated further increase of CRP level (231 mg/L) and increase of eosinophil count (1,600 cells/mcL, 10%), which reached 2,700 cells/mcL (14%) on day 8, but patient remained feverless and hemodynamic stable and new viral investigation and blood cultures were again negative. New echocardiography study indicated further improvement of left ventricular contractility (EF 50%), patient was started on low doses of beta blockers on day 8 and IABP was removed on day 9. On day 11, patient was discharged from the CCU maintain BP 110/70 mm Hg, and mean HR 90 beats/min in atrial fibrillation and on day 14 was discharged from the hospital on warfarin, metoprolol, amiodarone, digoxin, nifedipine, furosemide, diazepam and haloperidol.

Discussion

Most cases of myocarditis occurred within the first three weeks of therapy. Patients taking clozapine may present with like flu-like symptoms, fever, myalgia, dizziness or faintness, chest pain, dyspnoea, tachycardia or palpitations and other signs or symptoms of heart failure, consideration should always be given to a diagnosis of myocarditis[4]. The nature of clozapine induced myocarditis is related with the presence of eosinophilic and eosinophilia infiltrates in peripheral blood, and an acute IgE mediated (allergic type I reaction) hypersensitivity reaction to the drug has been proposed[5]. Cardiovascular adverse effects such as postural hypotension and tachycardia due to anti-cholinergic or alpha 1-adreneceptor blockade from clozapine are extremely common[6]. Clozapine also leads to other pharmacological effects such as blockade of calmodulin, sodium and calcium channels and alpha 2-adrenoceptors in the central nervous system or cardiac potassium channels such as human ether-Q-go-go related gene K^+ channel (HERG) and therefore has been shown to potentially induce arrhythmias and sudden cardiac death[7]. Decreased selenium concentrations in plasma and red cells were found to be significantly lower in patients with schizophrenia who were treated with clozapine as compared with all other neuroleptic groups which has been implicated in myocarditis and cardiomyopathy[8].

Conclusions

Considering that clozapine remains the gold standard in treatment of resistant psychosis there is an urgent need to raise awareness among medical and paramedical staff involved in the care of these patients.

Ethics

The research study adheres to the Code of Ethics of the World Medical Association.

Conflict of Interest

The Authors declare that there are no conflicts of interest.

References

1) Espino L. Varela-Casal P, Arauxo A. Clozapine-induce myocarditis. Actas Esp Psiquiatr 2008; 37: 243-244.
2) Kilian JG, Kerr K, Lawrence C, Celermajer DS. Myocarditis and cardiomyopathy associated with clozapine. Lancet 1999; 354: 1841-1845.
3) Haas SJ, Hill R, Krum H, Liew D, Tonkin A, Demos L, Stephan K, McNeil J. Clozapine-associated myocarditis: a review of 116 cases of suspected myocarditis associated with the use of clozapine in Australia during 1993-2003. Drug Saf 2007; 30: 47-57.
4) Hagg S, Spigset O, Bate A, Soderstrom TG. Myocarditis related to clozapine treatment. J Clin Psychopharmacol 2001; 21: 382-388.
5) Wooltorton E. Antipsychotic clozapine: myocarditis amd cardiovascular toxicity. CMAJ 2002; 166: 1185-1186.
6) Lee SY, Kim YJ, Kim KT, Choe H, Jo SH. Blockade of HERG human k+ channels and IKr of guinea-pig cardiomyocytes by the antipsychotic drug clozapine. Br J Pharmacol 2006; 148: 499-509.
7) Buckley NA, Sanders P. Cardiovascular adverse effects of antipsychotic drugs. Drug Saf 2000; 23: 215-228.
8) Vaddadi KS, Soosai E, Vaddadi G. Low blood selenium concentrations in schizophrenic patients on clozapine. Br J Clin Pharmacol 2003; 55: 307-309.