Repeated occurrence of clozapine-induced myocarditis in a patient with schizoaffective disorder and comorbid Parkinson's disease

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Abstract

Myocarditis is a rare but life threatening adverse effect of clozapine. Some symptoms of myocarditis – elevated temperature, tachycardia aWnd fatigue – appear commonly during the onset of treatment with clozapine and during the dose titration. We present a case of a patient with concurrent schizoaffective disorder and Parkinson's disease, who twice developed clozapine-induced myocarditis. All symptoms disappeared after the discontinuation of the drug. Early diagnosis, discontinuation of clozapine and supportive therapy of myocarditis lower the risk of a fatal outcome.

INTRODUCTION

Clozapine is an atypical antipsychotic indicated for the treatment of refractory schizophrenia. It is likewise used to treat psychiatric complications in Parkinson's disease (PD). Clozapine is the drug of choice in concurrent PD and a psychotic disorder (Urban *et al*. 2003). Clozapine is associated with hematologic and metabolic adverse events (Masopust *et al*. 2008). Less attention has been given to clozapine's adverse cardiac effects, including myocarditis and cardiomyopathy, despite a high associated mortality rate (Merill *et al*. 2006). We present a case of a patient who twice developed myocarditis induced by clozapine [Leponex].

CASE REPORT

The patient was 43-year old Caucasian male. Since 1987 when he was diagnosed with schizoaffective disorder, he has been treated with the first-generation antipsychotics. The first signs of PD occurred in 2002. Antipsychotics were discontinued but the Parkinsonian symptoms progressed and were still asymmetric. The finding of nigrostriatal degeneration by single photon-emission computer tomography (SPECT) confirmed the coincidence of Parkinson's disease and psychosis.

There was a relapse of psychosis in June 2004. The patient suffered from delusion of persecution and auditory hallucinations. This state was

CASE REPORT

Abbreviations:

BSA	– body surface area
CK	– creatine kinase
CK-MB	– creatine kinase MB isoform
CRP	– C-reactive protein
CT	– computed tomography
ECG	– electrocardiography
ECT	– electroconvulsive therapy
EF	– ejection fraction
FW	– Farheus-Westergreen
LV	– left ventricle
LV EDD	– left ventricle end-diastolic dimensions
PD	– Parkinson´s disease
SPECT	– single photon-emission computer tomography

improved by electroconvulsive therapy (ECT). Quetiapine [Seroquel] 800 mg/day was not sufficient to maintain this improvement. Quetiapine was switched to clozapine. The dose of clozapine was slowly titrated to 350 mg daily. On the twelfth day from the onset of treatment, fever, dyspnoea and tachycardia appeared. The leukocyte count was only at the higher limit of the normal range. The plasma level of the C-reactive protein was high: 188 mg/l. Serum troponin T level was found to be elevated at 0.48 ug/l. Chest X-ray and abdominal ultrasound and CT showed no pathological findings. The electrocardiographic (ECG) trace demonstrated sinus tachycardia 110/min. Heart ultrasound examination showed a dilated left cardiac ventricle, diffuse hypokinesis of the left ventricle and a decreased ejection fraction (EF) 40% (Table 1). Clozapine was discontinued due to a suspected role in the development of fever and cardiac symptoms. The antipsychotic medication included again quetiapine at 400 mg/day. The patient was discharged to home care in September 2004. One month later, another heart ultrasound examination was performed. The condition was restored to normal.

In November 2004 there was another relapse of psychosis. Quetiapine at 900 mg/day was ineffective and the patient was again started on clozapine. The administration of clozapine was consulted with a cardiologist. On the eleventh day (in January 2005) at the dose of 300 mg clozapine per day, fever, dyspnoea and tachycardia appeared once again. Pulmonary embolism was ruled out based on the measurement of D-dimers and a spiral lung CT. This imaging technique showed markedly thick myocardium of the left cardiac ventricle. Heart ultrasound showed the same findings as in August 2004 when a similar clinical picture was seen. Laboratory inflammation markers were within the same range as previously (Table 1). Heart scintigraphy showed a picture of myocarditis.

Due to suspected clozapine-induced myocarditis, we discontinued the administration of the drug. The patient was given antibiotics and his somatic state stabilised within a few days. After one month without any antipsychotic medication we started a therapy with olanzapine [Zyprexa]. A heart ultrasound examination performed in October 2006 showed only slightly impaired systolic function of the left ventricle with EF 50%.

The patient is currently in a relatively good psychic and physical state. His daily medication includes olanzapine 20 mg together with levodopa [L-DOPA] 500 mg and amantadine [Amantadin] 200 mg due to severe rigidity. He only rarely experiences auditory pseudohallucinations.

DISCUSSION

Our patient developed clozapine-induced myocarditis twice within 6 months. We observed identical clinical signs, laboratory parameters and heart ultrasound findings. All symptoms disappeared and heart ultrasound findings normalised after discontinuation of clozapine.

Kilian *et al.* (1999) reported 15 cases of myocarditis among 8 000 Australian patients treated with clozapine with 5 fatal endings. Cardiomyopathy was detected in 8 patients. The company Novartis (2003) received 213 spontaneous reports of clozapine-induced myocarditis with 50 fatal cases. In 85% of cases the symptoms appeared within the first two months of therapy. The drug was usually given in recommended daily doses. The risk of myocarditis is 17-322 times higher in patients treated with clozapine than in general population. In total, 231 cases of myocarditis and cardiomyopathy during the therapy with clozapine have been reported. Only 89 cases have been described in association with other antipsychotic drugs (Coulter *et al.* 2001; Merill *et al.* 2006). Haas *et al.* (2007) found in electronic databases 116 cases of suspected clozapine-related myocarditis in Australia during 1993-2003.

The causal relationship of clozapine and myocarditis has not yet been elucidated. According to Kilian *et al.* (1999), in some cases drug-induced myocarditis mediated by type I allergic reaction (IgE-mediated hypersensitivity) may be suspected. This then starts a cascade of production and secretion of pro-inflammatory mediators and prostaglandins. The bioactivation of clozapine to chemically reactive metabolites, which can be found in the myocardium, is another possible explanation. Other plausible mechanisms involve clozapine-induced cytokine release and hypercatecholaminemia. Clozapine in vivo stimulates release of tumor necrosis factor-alpha and various interleukins (Pollmächer *et al.* 2001; Merill *et al.* 2006). We did not find any evidence that myocarditis could be specifically related to the Parkinson´s disease in the MEDLINE database. The exact incidence of myocarditis in the Parkinson´s disease treated with clozapine is also not known.

The risk of myocarditis during the therapy with clozapine (and potentially other antipsychotics) should be taken into account when composing a plan for a long-term treatment. Clinical examination and ECG must be performed before the therapy with clozapine is started.

Table 1. Comparison of a clinical picture, selected laboratory results and imaging techniques in two consecutive cases of clozapine-induced myocarditis in one patient with schizoaffective disorder and Parkinson´s disease

Variable	August 2004	January 2005
Clozapine dose	350 mg daily	300 mg daily
Duration of treatment with clozapine	12 days	11 days
Symptoms	fever (max. 38.7 °C) dyspnoea tachycardia fatigue	fever (max. 38.2 °C) dyspnoea tachycardia fatigue
Examinations		
Heart ultrasound	LV dilation, LV EDD = 57 mm LV in systole/BSA = 30 (norm 14–21) LV in diastole/BSA = 36 (norm 21–32) LV hypokinesis, EF 40%, pericardial effusion: traces of fluid	LV EDD = 52 mm LV in /BSA = 24 LV in diastole/BSA = 31 ventric.septum hypokinesis, EF 45%, pericardial effusion: traces of fluid
ECG	sinus tachycardia 110/min.	sinus tachycardia 120/min.
Chest X-ray	normal findings	normal findings
Spiral chest CT	not performed	thick LV myocardium
Laboratory values [norm]		
FW [2–5/6–10]	30/50	42/75….6/8
Leukocytes [3.9–9.4 × 10^9/l]	9 ×10^9/l	8.8 × 10^9/l
Eosinophils [1–4 %]	2–6%	2.5–4 %
Neutrophil seg. [49–72%]	77%	70%
Lymphocytes [23–45%]	4%	11%
CRP [0–5 mg/l]	187…265…51 mg/l	162…2 mg/l
CK [1.03–3.53 ukat/l]	6…2.3 ukat/l	0.55…2.14 ukat/l
CK-MB [0–0.5 ukat/l]	0.53 ukat/l	low
Troponin T [0–0.03 ug/l]	0.48 ug/l	< 0.01 ug/l

BSA – body surface area, CK – creatine kinase, CK-MB – creatine kinase MB isoform, CRP – C-reactive protein, CT – computed tomography, ECG – electrocardiography, EF – ejection fraction, FW – Farheus-Westergreen, LV – left ventricle, LV EDD – left ventricle end-diastolic dimensions, LV in systole (diastole)/BSA – size of the cardiac compartment relative to the body surface area

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